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NO. 8. APRIL 1908

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THE TRANSFORMATIONS OF ELEMENTS

PART I.—THOSE DETECTED BY RADIOACTIVE METHODS; WITH SOME ACCOUNT OF THE PROPERTIES OF THESE ELEMENTS, SO FAR AS KNOWN

By ALEXANDER T. CAMERON, M.A., B.Sc.

University College, London

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Section 1.—Methods employed in the Detection of Radioactivity: Thorium and its Products

Radioactive substances are defined as those which possess the property of *spontaneously* emitting *radiations* or *rays* capable of passing through plates of metal, or other substances opaque to light. The word *ray* was first used in a definite sense by Newton, who employed it both in the sense of undulations and of corpuscles, in the latter sense especially in defending the old corpuscular theory of light. The rays, or radiations, emitted from radioactive bodies may be in like manner either corpuscular, or consist of undulations in the ether; both kinds are known. Such radiations possess certain characteristic properties. The most important are their penetrative power, emphasised in the definition, their action on photographic plates, and especially their property of discharging electrified bodies. The second of these properties first led to their detection; the last is the means most commonly employed in their study.

Cathode rays and *Röntgen* or *X-rays* possess such properties. So do the rays emitted under certain conditions by zinc sulphide and similar substances. They are not produced

spontaneously, however; the substances producing them are not radioactive.

In 1896 Henri Becquerel found that potassium uranyl sulphate emitted rays which acted on a photographic plate enveloped in black paper, and even separated from the uranium salt by thin plates of metal and other opaque substances. He found later that all the compounds of uranium, and the metal itself, possessed the same property. They not only appeared capable of giving off these radiations continuously, thereby giving rise to a continual supply of energy, but seemed perfectly unchanged by so doing. The action is spontaneous, and uranium is therefore the first element in which the property of radioactivity was discovered.

Uranium salts, besides acting on photographic plates, possess the other radioactive property of discharging electrified bodies. A charged *electroscope* consisting of strips of gold or aluminium leaf suspended from an insulated support, and separated from each other by the repulsion of their electric charge, is usually employed to test materials supposed to be radioactive. Not only is the electricity discharged by radioactive materials, but the rate at which the leaves fall together varies with the degree of radioactivity, other conditions being the same. Different uranium salts discharge an electroscope at different rates; they have different *activities*. Madame Curie has shown that this difference is due, primarily, to the varying proportion of uranium; the radioactivity is proportional to the percentage of uranium in the salt employed. When she extended these quantitative measurements to uranium minerals, this relationship was found to hold no longer. Certain varieties of pitchblende—which consists largely of uranium oxide—were four times as radioactive as the uranium they contained. Chalcolite, copper uranium phosphate, was twice as active; artificial chalcolite gave a figure agreeing with theory. These differences led M. and Mme. Curie to analyse systematically the mineral pitchblende, using the degree of activity as a test for every precipitate, and separating by repeated operations the radioactive from the inactive precipitates. In this way the two elements *polonium* and *radium* were isolated in 1898.

By similar methods during the last eleven years no fewer than twenty-four new elements have been discovered, most of

them radioactive. The history of science shows no parallel with the advance made in this subject. It is comparable with half a century's work in other directions of research. The advance is due in great part to the work of Prof. Ernest Rutherford, who has co-ordinated the facts by putting forward, and in part proving, the first reasonable theory to explain the great mass of data which is even yet accumulating.

The electrical measurements of radioactivity are made with some form of electroscope or electrometer. The electroscope devised by C. T. R. Wilson, and used largely for measuring

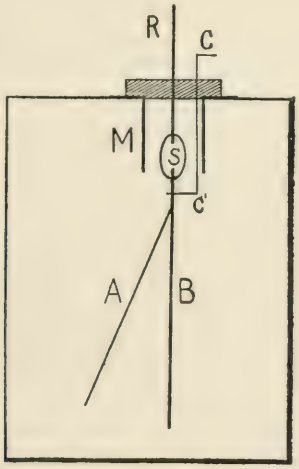

FIG. 1.

small amounts of activity, may be taken as typical. The description is that in Rutherford's *Radioactivity*, p. 86. A brass cylindrical vessel (or very frequently a tin can) is stoppered at the metal mouthpiece M (fig. 1) by an ebonite cork or an ordinary cork covered with sulphur. Through this passes a metal rod R, supporting a sulphur bead S, which supports and at the same time insulates a narrow brass plate B some two or three inches in length. To the upper end of the brass plate is attached a strip of gold, or better, aluminium, A. The sliding metal rod C C′ is used to charge the leaf system, usually by touching it with a charged rod of sealing-wax while it is in contact with B. R is earth-connected and C revolved to break the

contact with the brass and aluminium. The charged aluminium leaf is repelled through a considerable angle. Its movement is observed by a telescope through windows in the brass or tin vessel. The telescope carries a scale; observations are made of the time taken by the falling leaf to traverse a certain fixed portion of that scale. The bottom of the vessel is usually removable, the substances to be tested for radioactivity being thus introduced. In testing gases an airtight apparatus is used and the gases are introduced through metal stopcocks.

Under ordinary conditions, in the absence of radioactive matter the time taken by the falling leaf to pass over the fixed portion of the scale is termed the *natural leak* of the electroscope. This natural leak is quite considerable, and the time may even amount to several hours. The presence inside the case of a comparatively weak radioactive substance reduces the leak to a few minutes, or even seconds. It is desirable to give some account of the reasons underlying this behaviour.

An electroscope can be discharged readily through the action of several different kinds of energy. Thus rays of ultraviolet light allowed to fall on the outer disc of an ordinary electroscope, or the rays given out by a lighted candle placed near it, cause the leaves to fall together rapidly. X-rays behave similarly, and through a detailed study of their behaviour J. J. Thomson and Rutherford have put forward a theory capable of explaining the whole series of phenomena; so far it has stood the test of experience. The different rays are supposed to give rise to particles termed *ions* carrying either positive or negative charges of electricity. The initial action is a collision with an atom of the gas which the ray is traversing; an *electron*, or negative particle of electricity, is set free, the atom minus this electron exhibiting a positive charge. Both, by virtue of their charges, attract to themselves a cluster of uncharged atoms. The number in the case of the electron is estimated at about thirty; the positive cluster is smaller. Both clusters behave like ordinary charged bodies, being attracted by unlike, repelled by like, charges of electricity. Consequently in the absence of any strong electric charge in their neighbourhood they ultimately collide with each other, and their charges become neutralised. But if such ions are liberated in the neighbourhood of a charged

electroscope, it will attract ions with unlike charge in sufficient number to discharge itself (since the charge on the electroscope is likewise due to the presence of free electrons, if negative, or to free positive ions).

It is found that ordinary air always contains a certain very small number of ions, and the natural leak of an electroscope is due to their presence. Again, the production of ions is strictly proportional to the number of rays—*e.g.* if two quantities of uranium oxide are taken, one twice the weight of the other, and they are spread out in thin films of the same thickness, so that the first has twice the exposed area of the second, it will emit twice as many rays as the second; they will produce twice the number of ions, having twice the effect on the leaves of an electroscope; hence it will be discharged in half the time. Similarly if equal quantities of two radioactive materials are taken, and consecutively introduced inside an electroscope, and it is found that the rate of discharge of the first is twice as fast as that of the second, then it is said to possess twice the activity of the second. The measure of the discharge-time gives a measure of the radioactivity. By comparing the effect produced by a substance from day to day, a measure of the variation in its radioactivity is obtained.

The most convenient instrument for these measurements, however, is some form of quadrant *electrometer*, preferably the modification invented by Dolezalek in 1901. This has a very light needle of silvered paper, carrying a small mirror, and suspended by a very fine quartz fibre between the four quadrants. One pair is connected to earth, the other to an insulated metallic plate, facing a second which carries the radioactive matter to be tested. Through action similar to that in the case of an electroscope an electric stress is set up between the two pairs. The needle, previously charged to a very high potential, is repelled from one pair of electrodes towards the other; on account of its extreme lightness it moves at a uniform rate. The time taken to pass two fixed points is observed by means of a stop-watch. As in the case of an electroscope, this time is inversely proportional, other conditions being the same, to the degree of radioactivity of the deposit under observation. The natural leak of the electrometer is deducted from all other time measurements. The electrometer is standardised from time to time against a definite amount of uranium oxide, which is known

to give a constant supply of radiation. In this way any variations in the instrument are corrected.

The photographic action of the radiations has been largely used in certain branches of the subject, but does not give good quantitative results. The method employed is the exposure of the photographic plate wrapped in black paper—to cut off phosphorescent light—to the effect of the radiations. The time of exposure varies from a few minutes, with almost pure radium preparations, to perhaps seventy-two hours, with very weak radioactive preparations. With long exposures the results are especially untrustworthy on account of the difficulties experienced through the plates fogging.

In order to show how the instruments are actually employed and deductions made, a brief account will be given of the results obtained to the present time from the study of **thorium** compounds. The greater part is taken from Rutherford's *Radioactivity*, second edition.

Schmidt and Madame Curie independently discovered the radioactivity of thorium compounds in 1898. Four years later Rutherford and Soddy found that the thorium hydroxide precipitated by ammonia from a solution of the nitrate was less than half as active as the original solid salt; the filtrate on evaporation gave a residue which, weight for weight, was several thousand times more active. They named this active residue **thorium** X (ex-thorio). It consisted largely of impurities existing in the original nitrate; the true thorium X was present only in minute quantity, and could not be separated. It became inactive at the end of a month; in the same time the thorium completely regained its activity. They concluded therefore that thorium X was actually produced from thorium. They proceeded to study the time-rates of these processes, making electrical measurements at intervals over a long time. Their results are shown in fig. 2, A (*Radioactivity*, p. 221); the curves are typical of most of those illustrating the decay and production of radioactive matter. The initial activity of thorium X was arbitrarily taken as 100; similarly that figure was taken for the final activity of the thorium compound. The activities were expressed along the ordinates, the times from the initial measurement along the abscissæ. The initial irregularities in the curves were due to the presence in the original thorium compound of further

disintegration products of thorium X; these are also radioactive, and produce their own electrical effect. They were precipitated with the thorium hydroxide. The initial part of the *recovery curve* is due to their activity rapidly becoming smaller as they themselves disintegrate—more rapidly than is counteracted by the gradual reproduction of thorium X. The initial part of the *decay curve* is due to their reproduction from thorium X, when their activity gives an added effect to the activity of thorium X itself. In both cases a time is reached when in any given interval, say a minute, as much of these substances is produced as decays in that same time. These

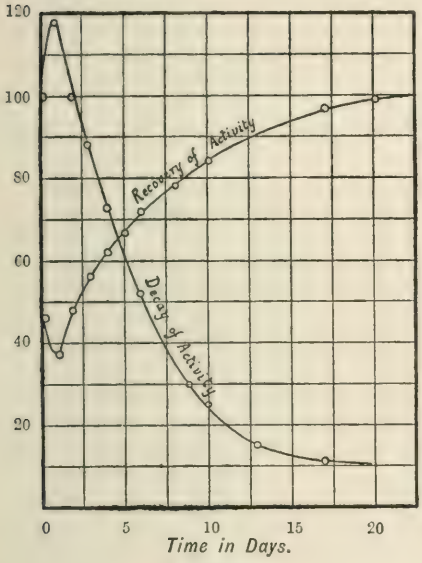

FIG. 2 A.

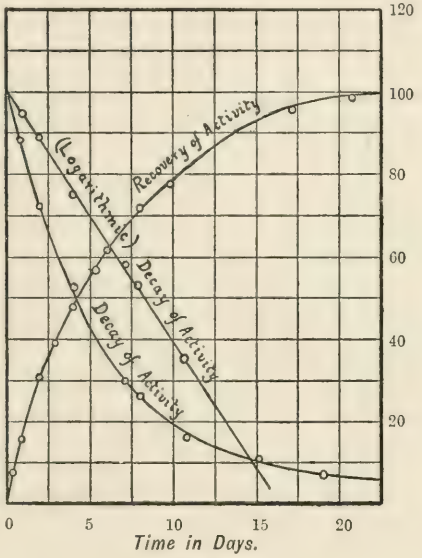

FIG. 2 B.

products are then said to be in *radioactive equilibrium*, and no longer affect the nature of the curve. The times in question are represented by the minimum and maximum on the respective curves, and it will be noticed that these exactly correspond. If the true curves are then continued back till they meet the axis, and the maximum values in both cases again taken as 100, the corrected values are shown in fig. 2, B (*Radioactivity*, p. 222). The decay curve is *logarithmic*, that is to say, if the logarithms of the activity values are plotted against time (instead of the true activity values), the result is always a straight line. This is shown in the figure. Such

logarithmic or *exponential* curves correspond to an equation of the type—

$$\frac{I_o}{I_t} = e^{-\lambda t} \quad . \quad . \quad . \quad . \quad . \quad (1).$$

In the case under consideration I_o is the initial activity of thorium X, I_t the activity after time t, λ is a constant, and e the natural base of logarithms ($= 2{\cdot}7183\ldots$).

The recovery curve is the inverse of this curve, and is represented by the equation—

$$\frac{I_t}{I_o} = 1 - e^{-\lambda t} \quad . \quad . \quad . \quad . \quad (2),$$

where I_o is the final activity (the maximum figure obtained), I_t the activity recovered after time t, and λ is the *same constant* as in the previous equation.

These results have been given in some detail because they are typical of most of the curves obtained by plotting the change of activity against time. In all cases the decay curve of the *radioactive child* bears the relation to its *radioactive parent* that the constant λ is the same for the two cases. The curves illustrate two further points. They approach constant value towards the end of a month, but it is seen that they reach a final value only at infinite time. This property is common to all such curves; it illustrates the fact that the *life* of a radioactive element is infinite. In order to compare such lives we therefore speak of the *half-life period*, a definite value for each element. It represents the time in which half the element disintegrates; its activity falls to half value. This time can be calculated graphically from the curves, or from equation (1), since the activity has fallen to half value, $I_o = 2I_t$, *i.e.* $2 = e^{-\lambda t}$. Hence if λ is known, t can be calculated. Again, λ represents the proportion of atoms changing per unit of time; $1/\lambda$ thus represents the *average life* of an atom of the element under consideration. A discussion of the meaning of these terms is given in Section 3 (p. 538). In the case of thorium X the half-time is four days.

Hahn has recently shown that thorium at first disintegrates into **mesothorium**, and this into **radiothorium**; the last named is the immediate parent of thorium X. Radiothorium is very much more active than the thorium from which it is derived. The methods employed were similar to those just described—

chemical separations, followed by measurement of the radioactivities of the different products.

Early workers on thorium noticed that the amount of radiation given off was subject to variation. Owens, in 1899, traced this inconstancy to air-currents passing over the surface of the thorium. Rutherford, next year, showed that it was due actually to a gas—hence the effect of air-currents. It could be drawn through tubes along with a current of air, passed through cotton-wool, bubbled through solutions, and gave thereafter an electrical effect. It thus behaved in every way like a true gas, although it could not be isolated, and could only be tested by its radioactive properties. Rutherford termed it an **emanation**. It has a very short-life period. Its decay was studied by drawing it into a cylinder by an air-current, closing the cylinder, and noting the radioactivity from time to time by the electrical method (the cylinder containing insulated metallic discs connected to an electrometer). Its half-life period is 54 seconds.

This emanation of course disintegrates into something else. When some quantity of it is allowed to decay in any closed vessel, the products are deposited on the walls of the vessel. They themselves give off radiations ; the phenomenon is known as *excited* or *induced activity*, the deposit as the *active deposit*. It differs in chemical and physical properties from all its predecessors. The emanation can be washed out with air, and the decay rate of the deposit studied. The curve is complex; mathematical analysis indicates at least two products. These were postulated as **thorium A** and **B**. They were differentiated more clearly by the work of Miss Slater, who studied the effect of temperature on them. A platinum wire was exposed for a considerable time to the action of the emanation, whereby (relatively) a considerable amount of the after-products was deposited on it. It was then heated by an electric current. A lead cylinder surrounding it caught any volatilised matter. Both wire and cylinder were then tested separately by an electrometer, the decay of the radioactivity being studied. Heated to about 700° C. the amount of radioactivity on the wire remained constant, but the decay rate was faster than usual. The cylinder was at first only very slightly active, but the activity grew rapidly, the maximum being reached in four hours; the decay rate thereafter was normal. These

phenomena were easily explained by the hypothesis that thorium A, the first product, volatilised below 700° and was *inactive—i.e.* gave no radiations; the thorium B, already produced from it, remained on the wire unvolatilised at 700°, and a fresh amount was slowly produced on the lead cylinder. Further work has slightly modified this result, thorium A being found to have a very slight radiation, and there being two later products, thorium B and C, all three having an extremely short-life period. The final product is inactive. So far as present knowledge indicates, the whole series is:

Thorium → mesothorium → radiothorium → thorium X → thorium emanation → thorium A → thorium B → thorium C → inactive product.

Most of the above work has been accomplished by what may be described as the *direct method* of work. In addition an indirect method, based on chemical means, is frequently employed. It will be discussed more particularly in the subsequent parts of this paper. An example will be mentioned here.

The final product of the uranium-radium disintegrations is supposed to be lead, another product being helium. Boltwood has analysed a great number of uranium minerals; they all contain lead. He finds that the ratio, amount of uranium to amount of lead, varies with the age of the mineral, the older rocks giving a higher percentage of lead. This agrees with the theory that lead is slowly produced from the uranium and radium. Strutt has analysed thorium minerals for helium; he finds evidence of some definite relationship between the quantities of thorium and helium which they contain.

Section 2.—Nature and Properties of the Radiations from Radioactive Elements

When an electric current is passed through a highly exhausted vacuum tube, three kinds of rays are produced in it. If the cathode is perforated, *canal rays*—so named by Wien—are projected with enormous velocity in the direction opposite to that in which the current is travelling; they consist of particles, each at least as heavy as a hydrogen atom, and always carry a positive charge of electricity. *Cathode rays*, consisting of negative particles of electricity, convey the current from cathode to

anode, while *Röntgen rays*, undulations in the ether, are projected in all directions. To these three kinds of ray correspond the three radiations which are emitted by radioactive matter. Like the canal rays are the *α rays*, heavy particles carrying a positive charge; the *β rays* are electrons like the cathode rays; while the *γ* rays strongly resemble Röntgen rays.

They are frequently emitted simultaneously from active preparations. Two properties allow of their study and differentiation:

(1) They behave differently under the action of a magnetic field;

(2) Different kinds of rays penetrate matter to very different degrees.

Under ordinary conditions all these rays, like light rays, travel in straight lines. Under the action of a very strong magnetic field the path of the *α* rays becomes slightly curved; *β* rays are much more easily deflected, and, moreover, in the opposite direction to *α* rays—compare the fact that *α* rays carry a positive charge, *β* rays a negative one; *γ* rays are not deflected by a magnetic field.

The difference in penetrating power is well shown by the following table (Rutherford, *Radioactivity*, p. 111):

Radiation.	Thickness of Aluminium in cms., which cuts off half the radiation.	Relative power of penetration.
α-rays	0·0005 cms.	1
β „	0·05 „	100
γ „	8 „	10000

These ratios are only approximate; rays from different material have greatly varying penetrative power. Different substances absorb them in widely different amounts; the density of the substance is a factor in determining the amount of absorption.

The radiations—as has been pointed out in Section 1—produce ions in the gases they traverse; the mechanism is collision. Their ionising power varies very greatly, being roughly the inverse of their penetrability.

The enormously greater ionising power of the *α* rays supports the theory that they are heavy particles shot off from

the disintegrating atoms at enormous velocities. Such large particles cannot travel far without colliding with gas particles, hence their small penetrative power. Their enormous momentum produces the correspondingly great ionising effect actually observed. Rutherford has measured the velocity of α particles from different active elements; it varies from $1{\cdot}56 \times 10^9$ cms. per second in the case of radium to $2{\cdot}25 \times 10^9$ cms. per second for thorium C. Light travels at about 30×10^9 cms. per second. The experiments lead to the conclusion that the substances possessing longest life, viz. uranium and radium, emit particles having the least velocity; the shorter the life the greater the velocity of the emitted α ray. Rutherford has been able to measure the mass of the particle which carries unit charge of electricity; it is about twice that of hydrogen. From this he concludes that the α particle consists either of a half atom of helium (atomic weight 4) carrying one electric charge, or a whole atom carrying a double charge. The α rays carry a positive charge—their mass and velocity correspond very closely with those of canal rays; their close resemblance to these must be held as established.

The β rays have a greater range of velocity. The maximum velocity approximates to that of light (200,000 miles per second). Their identity with cathode rays has been established on three grounds: (*a*) the negative electric charge carried by both; (*b*) the ratio of that charge to the mass—extremely small in both cases—which carries it; and (*c*) the fact that a magnetic field has precisely the same effect in both cases.

α and β rays are completely absorbed by covering the radioactive matter producing them with a layer of lead 1 cm. in thickness. But even if a layer of 1 inch is used, rays still pass through. They carry no charge of electricity, and are not deflected by a magnetic field, yet they ionise gases, and so affect an electrometer. These are the γ rays, ether waves, corresponding to X-rays, but of even greater penetrating power.

All three kinds of rays on impinging on solid particles give rise to *secondary rays*, as do ordinary X-rays. The secondary rays also travel in straight lines, and otherwise obey the light laws, but are deflected by a magnetic field. They resemble cathode rays in being electrons, but move with comparatively small velocity. Ultra-violet light allowed to fall on the surface of metals produces a similar phenomenon.

In examining a radioactive substance to find what kind of radiations it gives rise to, the method in use is to cover it with varying thicknesses of aluminium. Absorption takes place to different extents; the ionisation varies accordingly; this is recorded by electric measurements. From a study of results thus obtained it can usually be determined whether one or more kinds of ray are present; the results are confirmed by noting the action of a magnetic field on rays which have penetrated the different thicknesses of metal.

The radiations produce a considerable number of effects—physical, chemical, and physiological. One of the most important is the phosphorescence induced in many substances subjected to bombardment by the rays. Zinc sulphide, a particularly good example, is rendered luminous by both α and β rays. Crystals of the different platinocyanides give different colour effects according to their composition. The lithium salt phosphoresces pink, the calcium and barium salts deep green, the sodium salt yellow. Willemite, a zinc silicate, becomes beautifully green in colour and apparently translucent. Kunzite shows a red phosphorescence under the action of β and γ rays; α rays are without effect on it. All strongly radioactive compounds phosphoresce strongly themselves.

The diamond not only phosphoresces when bombarded by radium rays, it also changes colour. Sir William Crookes found that a yellow diamond, after seventy-eight days' exposure to the rays, became bluish green. Prof. Bordas has recently experimented with uncoloured rubies; after some weeks' exposure they became dark brown, and in some cases pink; sapphires similarly change colour. The effect is in all these cases probably due to the action of β rays, and is analogous to their action on different glasses. Soda glass is coloured deep violet, potash glass a dark brown, gold glass ruby colour. Similar effects are produced by cathode rays in vacuum tubes. The colour is discharged quite easily by heating the glass to 300–400° C. Maxwell Garnett has made a detailed study of these phenomena, and his work supports the hypothesis that metallic ions are actually liberated in the glass, and that the colour is due to these, violet for sodium, brown for potassium, and so on; application of heat causes recombination with accompanying loss of colour. It should also be mentioned that glass tubes containing radium emanation show a beautiful

green phosphorescence. Under similar conditions quartz glass shows a fine electric blue colour.

The rays change oxygen into ozone. Hence all dry radium salts smell strongly of ozone. In water this effect is not produced, hydrogen peroxide being formed instead. Radium salts and its emanation decompose water. The emanation also effects the recombination of hydrogen and oxygen. These phenomena are in all probability produced by the α rays.

Under the action of β rays yellow phosphorus is converted into the red variety, while iodine is liberated in iodoform solutions. Much work yet remains to be done in this branch of the subject.

Radium rays, like X-rays, produce painful burns. Painful irritation is caused, then inflammation lasting from ten to twenty days. The skin finally peels off. The physiological effects of radium emanation have been tried on mice and guinea-pigs. Long exposure to such treatment is in most cases harmful, in some fatal. Radium rays have a beneficial result in the case of ulcerous growths, but do not cure true cancer. Their effects are thus similar to those of X-rays, but they have the advantage that the radium preparation, enclosed in a small tube, can be applied locally. The medicinal effects of many natural waters are supposed to be due to the presence of small quantities of radium emanation. They are slightly radioactive. Artificial waters of exactly the same chemical composition do not possess the same beneficial effect.

Section 3.—Life of a Radioactive Element

A typical radioactive element gives rise continually to a radioactive product, together with one or more kinds of rays; radium gives rise to its emanation, and to α rays. In addition, heat in comparatively large quantity is continually liberated.

This continuous production of both energy and matter is explained by Rutherford by the assumption that atoms of the parent element are continually being broken down, or disintegrated, into simpler atoms, the heat and rays being the difference in energy-content in the two atomic systems. When guncotton is exploded a complex molecule is broken up into simpler ones, heat and light being also emitted. The two cases are parallel, the one being atomic, the other molecular.

It is found that the emanations, and many other active products, lose their activity almost completely in a measurable time. From studies of the rate at which the activity is lost, the conclusion is reached that in any one time a certain fixed proportion of the total number of atoms present spontaneously disintegrates. An actual illustration will make this clearer. The activity of any fixed quantity of radium emanation falls to half the initial value in approximately four days. In the second four days it falls to half of this second value, *i.e.* one quarter of the original. We therefore suppose that the emanation has decomposed to a corresponding extent. In the unit of time chosen, four days, the same quantity, one-half the amount at the beginning of that period, always disappears. Similarly in any other definite period of time a certain quantity, bearing a definite ratio to the original amount, will disappear. Again, at the end of eight days one quarter of the whole amount remains; at the end of twelve days, one-eighth; of sixteen days, one-sixteenth. But at the end of infinite time there will always remain some quantity, however small. Similarly in all cases of active matter some remains undisintegrated after infinite time; the radioactive elements have an *infinite life*. Though they may have *died* for all practical purposes at the end of some measurable time, an unmeasurable but definite amount remains. However, it has been shown in Section 1 (p. 532) that we can always find when half a given quantity of active substance has disappeared. And it is this period which is termed the *half-life period* of such substances. It varies from four seconds in the case of actinium emanation to millions of years in the case of uranium.

Another term constantly used is the *average life* of a substance. In Section 1 the method of calculating it has been given (p. 532). It can be conveniently illustrated by a human parallel. A church filled with people on any fixed date contains a fair assortment of men, women, and children of all ages. If we know the total number of years each person will live after leaving that church we can calculate the *average life* of the congregation counting from the definite time fixed by that church attendance. This is quite different from the *average life* of some number of persons from the time of birth of each, which is the basis of the data employed to calculate insurance rates.

The *average life* of a radioactive element at any definite time corresponds to the first of these illustrations. If we take a definite quantity of radium salt, then the atoms of radium it contains are of all ages. If they have just previously been separated from their uranium ore some may have been *born* only a few weeks previously, others have existed thousands of years, just as the church congregation may include infants and old men of ninety. Of the radium atoms a certain number will *expire* in a definite time, just as in so many years a number of the worshippers will have died. And we can calculate the average life of the congregation of atoms with as much certainty as that of people.

The application of the second kind of *average life* to radioactive substances was recently worked out in some detail by Sir William Ramsay as a lecture illustration. Though it has just been stated that the life of a radioactive atom is infinite, yet infinity is only a relative term; in this connection it only means a longer time than we can measure. It is extremely probable that just as the human life is measurable and definite, so is, let us say, the life of an atom of radium. One may go further. For there is much more regularity in the life of this dead matter; the life of human beings is variable, dependent on "all the ills that flesh is heir to," microbes, the bearers of disease, and accidents, the ills of fortune. We have no ground to suppose that the life of a radioactive atom varies from any similar cause. For example, the rate of decay—the death-rate—of radium emanation is unaltered within the limits of measurement between the temperatures of $-180°$ and $+1600°$ C. ($90-1870°$ in the absolute scale), the extremes at which, so far, it has been experimentally tested. If this tremendous difference of temperature does not hasten the decay of a single atom of emanation we can at least postulate that its life is not easily influenced by external causes. So far experimental work has shown that we cannot hasten or retard the death of a radioactive atom; consequently we cannot alter its life. For its birth is but the death of its parent atom, to which the preceding statement likewise applies. And we are justified in stating that the average life of a radioactive atom, as used in the second sense above, is in all probability the actual life of that atom.

Section 4.—Radioactive Elements and their Properties

No fewer than twenty-four new elements have been discovered by radioactive methods; uranium and thorium were known long before their activity was observed. Of these twenty-six elements, five are said to be *rayless*; in them no activity has been detected by the instruments in use at present. The others emit one or more kinds of ray; nine or ten give α particles alone. An appreciable life-period is possessed by nine only—uranium, thorium, radium, polonium, radio-lead, mesothorium and radiothorium, actinium, and probably ionium. The remainder are none the less true elements, although their short life may never permit them to be examined by other than radioactive means.

If the recent work of Boltwood is correct, and ionium is the true intermediate product between uranium X and radium, these twenty-six elements fall naturally into three large groups, namely, the elements uranium, thorium, and actinium, and their respective disintegration products. Using Rutherford's method of classification (from *Radioactivity*, pp. 449-50) in a slightly modified form, the elements can be grouped as shown below. Only the atomic weights of three—uranium, radium, and thorium—are known with any certainty. If the α particle is a helium atom (of atomic weight 4), then the atomic weights of the other elements, calculated by deducting 4 for each α particle evolved, may approximate to those given in brackets. The present state of our knowledge does not allow any stress to be placed on this hypothesis. In the table on the next page Ur = uranium, Th = thorium, Ra = radium, Act = actinium.

The nomenclature of the elements is due to Rutherford; his original idea was to name the first derivatives so as to show their parentage; hence Ur X, Th X, Act X (ex-uranio, ex-thorio, ex-actinio). The discovery of radiothorium and radioactinium upset this system. It will be observed that each group contains one gas or emanation; the elements derived from it are named in order of formation A, B, C, and so on. The graphic representation in the last column, due to Rutherford, illustrates the method of disintegration, the atomic contractions due to loss of α particles being considerably exaggerated in order to emphasise the theory. The brackets show those elements which differ in mass content by not more than one electron.

Element.	Atomic Weight.	Half-Life Period.	Nature of Emitted Rays.	Exaggerated Graphic Representation
First Group:				
Ur	238·5	—	α	
↓				
Ur X	(234·5)	22 days	$\alpha\beta\gamma$	
↓				
Ionium	(230·5)	—	$\alpha\beta\gamma$	
↓				
Ra	226·5	1300 years or 164 ,,	α	
↓				
Emanation	(222·5)	3·8 days	α	
↓				
Ra A	(218·5)	3 minutes	α	
↓				
Ra B	(214·5)	21 ,,	rayless	
↓				
Ra C	(214·5)	28 ,,	$\alpha\beta\gamma$	
↓				
Ra D	(210·5)	40 years	rayless	
↓				
Ra E	(210·5)	6 days	$\beta\gamma$	
↓				
Ra F	(210·5)	143 ,,	α	
↓				
Inactive Product	(206·5) Cp. lead = 207	—	rayless	
Second Group:				
Th	232·5	—	rayless	
↓				
Mesothorium	(232·5)	5·5 years	β	
↓				
Radiothorium	(232·5)	737 days	$\alpha\beta\gamma$	
↓				
Th X	(228·5)	4 ,,	α	
↓				
Emanation	(224·5)	53 seconds	α	
↓				
Th A	(220·5)	11 hours	slow β	
↓				
Th B	(220·5)	55 minutes	$\alpha\beta\gamma$	
↓				
Th C	(216·5)			
↓				
Inactive Product	(?)		rayless	
Third Group:				
Act	?	—	rayless	
↓				
Radioactinium		19·5 days	α	
↓				
Act X		10·2 ,,	α (β?)	
↓				
Emanation		3·9 seconds	α	
↓				
Act A		36 minutes	rayless	
↓				
Act B		2·15 ,,	$\alpha\beta\gamma$	
↓				
Act C		?		
↓				
Inactive Product		—	rayless	

A short account of the individual elements will now be given, in the order shown opposite.

Uranium was discovered by Klaproth in the mineral pitchblende in 1789. It is of comparatively rare occurrence, and widely scattered. The composition of uranium minerals varies largely; many are complex silicates, phosphates, or arsenates. Pitchblende and uraninite consist largely of uranium oxide, and contain from 50–80 per cent. uranium. The metal was isolated by Peligot in 1842 by the action of potassium on the fused oxide. Thus formed it is a black powder. In the ordinary metallic state it closely resembles iron and nickel. Heated to redness it burns brilliantly. It dissolves in dilute acids, with evolution of hydrogen; combines directly with chlorine, and, on heating, with sulphur. Its atomic weight is 238·5; it is thus the heaviest metal yet isolated. A great number of its compounds have been prepared. The discovery of radioactivity by Becquerel, in 1896, was made with these compounds; it has been shown that the metal is also radioactive. The life of uranium is extremely great. Its half period is many millions of years.

In 1900 Sir William Crookes showed that when excess of ammonium carbonate is added to a uranium solution, until the uranium precipitate has all redissolved, a light cloudy precipitate remains: this contains all the photographic activity; the separated uranium is without effect on a photographic plate (α rays do not affect a photographic plate; uranium gives off α rays only); Crookes called the new product **uranium X**. The precipitate consists largely of impurities from the uranium salt, and insufficient uranium X has been obtained to give a distinctive spectrum. A mixture of ether and water effects a partial separation. The ether layer contains most of the photographic or β-ray activity. Becquerel effected a separation by adding barium chloride and precipitating the barium as sulphate; uranium X is carried down along with it. Recently (in 1906) Moore and Schlundt have described further methods of separation. When crystallised uranium nitrate is dissolved in acetone, or several similar organic solvents, the slight precipitate which remains contains most of the uranium X. Complete separation is effected by adding moist ferric hydroxide to such a solution; the hydroxide carries down all the active matter. Moore and Schlundt state that uranium X gives both α and β rays; 34 per cent. of the activity is due to the α-rays. Levin

in 1907 obtained the figure 8 per cent.; in a later paper he states that no α rays are produced, the mistake arising from the presence of β rays of small velocity. The question has not yet been decided. Uranium X has a half-life period of twenty-two days. In less than a year it has disintegrated almost completely. Into what has it changed?

Ever since Madame Curie succeeded in obtaining radium from uranium minerals, and the theory of disintegration was put forward, it has been considered highly probable that radium is a *descendant*, in perhaps the third or fourth generation, of uranium itself. Some experiments of Soddy in 1904 gave the first proof of this statement. He took about two pounds of uranium nitrate, dissolved it in water, and repeatedly added barium solution, precipitating the barium as sulphate. In this way the solution was practically freed from radium, which is precipitated along with the barium sulphate. In 567 days the solution contained more than one hundred times as much radium as it did immediately after this treatment. This radium was identified by the decay rate of its emanation. The actual amount of radium observed was only one-thousandth of what it should be on the assumption that uranium X was the parent of radium. Soddy postulated one or two intermediate products. Boltwood criticised his method of procedure but afterwards confirmed his results. In 1906 he suggested that the intermediate product was actinium. Soddy and Mackenzie, and also Rutherford, showed that this was impossible, pure uranium nitrate neither giving rise to actinium nor its emanation. Rutherford separated the actinium from solutions of commercial uranium nitrate, and by passing ammonia and sulphuretted hydrogen gases through the actinium solution, he effected the separation of a new radioactive substance, which he considered to be the actual intermediate product between uranium X and radium. Boltwood confirmed this result. He found this new element emits α rays (actinium is rayless) which are very easily absorbed, and β rays of small penetrability. The activity is of the same order as that of radium. He suggested the name **Ionium**. Hahn has confirmed his conclusion by a different method.

Radium was discovered by Madame Curie in 1898. Her method of procedure has been indicated. Thoroughly examining the different group precipitates in an analysis of pitchblende, she found that the barium group precipitate was strongly active.

This activity could be completely separated along with barium sulphate. Final separation was effected by recrystallising the barium as chloride; radium chloride is slightly less soluble and separates in the first fraction. In this way crystals were finally obtained nearly two million times as active as uranium. The activity was too great for comparative measurements; the final fractions were tested for purity by estimating the amount of barium spectroscopically.

Giesel showed later that the separation could be effected more conveniently by recrystallising the bromides; the difference in their solubilities is greater than in those of the chlorides.

Radium continually gives rise to a gas, the **Emanation from Radium**, discovered by Dorn in 1900, and no intermediate product has yet been detected. A full account of the properties of radium and its emanation will be given in Part II. of this paper.

When any substance is exposed to the action of the emanation it becames coated with an intensely active deposit. This was first observed by M. and Mme. Curie in 1899. It is known as the **active deposit of rapid change**, and has been found to consist of three consecutive products, **Radium A, B, and C.** The whole activity decays to half value in 28 minutes, but the decay curve is very irregular. Studies of the rates of decay of the different rays led to the analysis into three separate elements. All three are soluble in strong acids, and volatile at a white heat. B is volatile at the lowest temperature, and can be thus partially separated.

In 1903 the Curies also observed that substances which have been covered with this active deposit do not lose all their activity after even a prolonged period. Giesel confirmed this. Rutherford found that the activity increases during several years. It is due to the **active deposit of slow change**, which has been resolved similarly into three consecutive products, **Radium D, E, and F.**

Radio-lead (or Radium D) was obtained by Hofmann and Strauss in 1901. The lead obtained from pitchblende was strongly and permanently radioactive—hence the name radio-lead. In 1904 Hofmann and co-workers showed that the lead itself is not radioactive, but gives rise to active products separable by chemical means; the inactive lead slowly regains activity. It therefore contains an inactive element which disintegrates slowly into active products. Rutherford has proved fairly conclusively the identity of the rayless parent, the true radio-

lead, with radium D, and of the active products with E and F. He found that the activity of the short-life deposit from radium practically vanished after two days; thereafter there was a slow increase during eighteen months. The new activity was due to both α and β particles. Two experiments showed the nature of the changes. A deposit on a platinum wire, after standing for some considerable time, was subjected to the action of heat. Below 1000° it was unaffected. Between 1000° and 1050° some part volatilised. It no longer gave off α particles, while the β-ray activity decreased rapidly, falling to half value in six days. During the same time α rays were emitted in slowly increasing amounts.

Clean surfaces of metallic bismuth placed for some time in solutions of the slow-change deposit removed 90 per cent. of the substance emitting α particles. The bismuth thereafter emitted these α particles, activity decreasing somewhat slowly; the half-life period was 143 days. The β-ray activity of the solution remained unaltered by this treatment; after the bismuth was taken from the solution the latter commenced slowly to emit α rays.

A simple explanation is given by the assumption of three elements: radium D (rayless); E, giving β rays only; and F, giving α rays only. D is volatile below 1050°; E does not volatilise at that temperature. D is the parent of E, for after it has volatilised the amount of E rapidly becomes less. F volatilises at 1050°, for the wire loses its α activity. It is produced from E, for the α activity of the wire is slowly regained. F, alone of the three, is deposited on bismuth from solutions, and it is the element whose half-life period is 143 days.

Meyer and Schweidler consider that this hypothesis does not completely satisfy the peculiarities of the curve of decay. They suggest a further intermediate product (thus RaE_1 and RaE_2).

Rutherford has shown the identity of **polonium, radio-tellurium,** and **radium F**. Polonium was the first radioactive substance discovered by Madame Curie. The sulphide precipitate from acid solutions of pitchblende contained an active substance, which associated itself with bismuth. With this element its properties are so closely allied that it is impossible to effect a complete separation. Madame Curie repeatedly precipitated the nitric-acid solution by water. The precipitate contains most of the active material. Marckwald obtained the same substance by dipping a rod of bismuth or antimony in the

active solution. These formed an intensely black deposit, chiefly tellurium, and very active; he named the active matter radio-tellurium. Dissolved in hydrochloric acid, all the tellurium was precipitated by hydrazine hydrochloride; the active matter remained in solution. By repeating the process, Marckwald obtained a few milligrams of intensely active material.

There remains the question of the final product. Radium F decays at a moderately rapid rate. What becomes of it? Two lines of argument point to the conclusion that **lead** is formed. On the assumption that the α particle is helium of atomic weight 4, then, since α particles are given out by radium and four of its products, the atomic weight of the final product should be $226{\cdot}5 - (5 \times 4) = 206{\cdot}5$. Lead has the atomic weight 207, a very close agreement.

Again, Boltwood has shown that lead is present in all uranium-radium minerals, and the amount is greatest in the oldest—*i.e.* those in which the greatest quantity of uranium has disintegrated. This also points to the fact that the lead is derived from uranium, and therefore from radium.

Thorium was discovered by Berzelius in 1828. It occurs chiefly in Ceylon, the recently discovered mineral thorianite containing more than 70 per cent. of it. It is precipitated from solution by ammonia, and usually separated in the form of oxalate. The metal has been prepared as a grey powder; it burns brilliantly in air, and is easily dissolved by warm, dilute acids. The oxide ThO_2 is usually obtained by calcining the oxalate or sulphate. A large number of the salts have been prepared.

An account of the disintegration changes of thorium has been given in Section 1 (pp. 530-534). It need only be mentioned here that the emanation is an inert gas strongly resembling the gases of the argon group, while the activity of radiothorium is several hundred thousand times that of thorium itself. Rutherford suggests that the final disintegration product of thorium may possibly be bismuth.

Actinium was discovered by Debierne in 1899, and independently as *emanium* by Giesel in 1902; it is precipitated with the group of cerium earths, and is closely allied to lanthanum. It is many thousand times more active than thorium; although it strongly resembles that element, yet all the products of the two have entirely different decay rates—a sufficient proof of their separate identities.

Hahn, in 1907, succeeded in showing that actinium is rayless, its activity being due to its first product **radio-actinium**; this gives *a* rays only, corresponding to radiothorium. According to Giesel it resembles the alkaline earth metals, and can be precipitated from actinium solution by means of finely divided sulphur. It disintegrates into **actinium X**, independently discovered in 1905 by Giesel and Godlewski; the separation is similar to that employed for thorium X. The emanation was observed by both Debierne and Giesel; Godlewski proved that actinium X was its immediate parent. Debierne has recently noted the production of helium from this emanation; Giesel has confirmed the statement. The analysis of the active deposit from the emanation is in great part the work of Miss Brooks. Her work led to the recognition of **actinium A** and **B**; Meyer and Schweidler consider that **C** and **D** also exist.

So far we have no clue to the atomic weight of actinium. But it corresponds to lanthanum; in that case it either comes between radium and thorium, with an atomic weight of about 230, or has a greater weight than uranium. Actinium emanation most probably belongs to the argon series, in the periodic system, when it follows that radio-actinium corresponds to radium (it resembles the alkaline earth metals) and actinium X occupies the space below gold. With similar treatment of the thorium products we can postulate some such arrangement as the following for the higher members of the periodic system; it accepts the simplest hypothesis of disintegration—that it is accompanied by loss of mass.

Kr 87·8	Rb 85·4	Sr 87·6	ϒ 89	Zr 90·6	Cb 94	Mo 96	...	Ru 101, Rh 103, Pd 106·5
...	Ag 108	Cd 112·4	In 115	Sn 119	Sb 120	Te 127·6	I 127	...
X 128	Cs 133	Ba 137·4	La 139	Ce, etc., 140-178	Ta 183	W 184	...	Os 191, Ir 193, Pt 195
...	Au 197	Hg 200	Tl 204	Pb 207	←RaF← Bi 208·5	(?RaE)←	(??RaD)← ? ← ? ←	(RaC) ←(RaB) ←(RaA) ← (ThC) ←(ThB) ←(ThA)← (ActC) ← (ActB) ←(ActA)←
Ra Em ← Th Em ← Act Em←	← Th X ← Act X←	Ra 226·5 Radioth ← Radioact←	← Mesoth ← Act	Ionium← Th 232·5	UrX ←	U 238·5		

There are several difficulties in the way of accepting such a scheme. For example, radium D has given no indications of any resemblance to the halogens; on the contrary it strongly resembes lead. Although such hypotheses must therefore be put forward very tentatively, we can scarcely evade the conclusion that many higher members of the series have almost coincident atomic weights, while there are several cases of at least two elements occupying one space in the table. Thus, considering the radium and thorium products alone, their emanations are both inert gases strongly resembling the argon gases. To move one a space higher in the series, the difference in their atomic weights must be at least 25. If the hitherto published chemical work on the atomic weight of radium is in any way near the truth, this cannot be the case. Similarly radium F must have an atomic weight less than radium, and it closely resembles bismuth in all its properties. If the atomic weight of radium is 226·5, it seems certain that bismuth and radium F must occupy the same space. There are only two other possibilities. A somewhat similar table, put forward by Meyer and Schweidler in 1906, assumes that uranium contains in reality a second element of much greater atomic weight, about 260, and that radium has the corresponding weight 255. In the second place, disintegration may result in the combination of two or more atoms of the product, giving an element of higher atomic weight; in this case, the active elements will not appear in consecutive series in the periodic table.

The second part of this paper will contain a full account of radium and its emanation.

The third part will include a description of the experimental production of transformation or transmutation of elements.

THE ACTION OF ALCOHOL[1]

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It is but seldom in the study of medical science that one has to treat of a question of such widespread interest, and, as I believe, of such paramount national importance as we have before us to-day, and it is to be deplored that the medical profession has hitherto been able to answer only with uncertain voice, or, I might say, with two voices, the persistent demand for its opinion of the value of alcohol in therapeutics and in diet.

This fatal lack of unanimity is to be ascribed in the first place to the feeling that alcohol has not proved devoid of usefulness in therapeutics in the past, and that we must not be hurried into its dismissal from the sphere of medicinal agents without due consideration; and the denial of its value in disease has been in many cases too absolute, and has, in fact, provoked a reaction in its favour in some minds that were perhaps prepared to accept a more restricted use of alcohol as a remedy than has hitherto prevailed. The greatest possible advance in the crusade against the abuse of alcohol would be made, I think, if we could agree upon some formula that could be generally accepted, and I am not without hope that this meeting may make some progress towards this solution.

Another cause of confusion in the response of medicine to inquiry regarding the value of alcohol arises from ambiguity in the use of terms. We are too apt to apply the term "stimulant" to anything that promotes exhilaration and animation, and dissipates what the eighteenth century called the spleen, and to regard the result as evidence of health and vigour. But stimulant is also used, in a more exact sense, to indicate anything augmenting the activity of definite organs. It would, I think, conduce to more general agreement if the word could

[1] A paper read before the Section of Physiology at the British Association, Leicester, 1907.

be used strictly in this narrower sense in discussing the question of alcohol, and if its effects, beneficial or otherwise, were always referred to each individual organ.

Alcohol affects so many functions of the body that it is impossible to take them all up in the time at my disposal, and I shall therefore limit my observations to its action on nutrition, on the brain, and on the circulation.

Its effects on nutrition are ascribed in part to its influencing the digestion and absorption of ordinary foods, and in part to its acting as a food itself. As to the first, its effects on the digestive processes, there is a very general belief, supported by apostolic authority, that alcohol improves digestion. A large number of painstaking investigations have been carried out without fully confirming the popular view, however. It is true that the digestive ferments have been found to be accelerated by very small quantities of pure alcohol, but the acceleration is very small in degree, and is not observed when the forms of alcohol in ordinary use are substituted for the pure spirit, nor when this itself is added in quantities corresponding to one to two glasses of whiskey in man. As to the secretion of the digestive fluids under alcohol, it has been repeatedly found that alcohol after absorption induces a flow of gastric juice, but this is devoid of, or poor in ferments, and can scarcely promote the preparation of food for absorption. The movements of the stomach and intestine may perhaps be more active after alcohol has been swallowed in a concentrated form, and this may perhaps be the basis of the after-dinner liqueur. And some evidence is presented that alcohol accelerates absorption from the intestine, as is true of many other slightly irritant bodies.

The effects of alcohol on the digestion are therefore complex, for almost every factor in the process is altered in activity to a small extent when moderate quantities are taken. When one remembers, in addition, that the greatest influence of all on digestion is exercised by the taste and odour of the food, one is prepared for great divergences in the effects of alcohol in man. And this is the only inference that can be drawn from the results of clinical inquiry as to the value of alcohol as a stomachic in man. In some people the progress of digestion seems to be rather improved when wine is taken, but the improvement is small, while in others the reverse is true: the digestion is not accelerated, and may even be retarded by a

couple of glasses of wine. The actual amount of food absorbed from the alimentary tract is scarcely changed definitely in either direction. But however variable the reaction of the individual stomach to small quantities of alcohol may be, there is only one response when larger quantities are taken, and that is disorganisation of the whole process. And while the usefulness of alcohol in treating some digestive disorders may still be uncontroverted, Binz's dictum, that the healthy stomach needs no stomachic, and therefore no alcohol, must be the standpoint of the physician to-day.

But it may be argued that while the absolutely normal stomach is capable of digesting thoroughly and extracting the whole of the nutriment from the food offered to it, the artificial conditions under which most of us live necessitate measures which are unnecessary in a more healthful environment. Does not the jaded appetite demand exceptional measures, and may not wine be used to render food palatable and promote gastric secretion and digestion just as other condiments are employed? Shall he who seasons his food with wine be condemned, while he who substitutes mustard may be regarded as of upright life and conversation? The objection to the habitual use of alcoholic beverages "for the stomach's sake," in the scriptural phrase, does not arise from its effects on the digestion, but from the tendency towards the habit being formed and from its action on the brain.

In regard to the second phase of the question of alcohol on nutrition—its food value—the last few years have witnessed experiments performed with such meticulous care that there can be but one opinion in the minds of those who have studied the subject. Over 95 per cent. of the alcohol ingested undergoes combustion in the tissues and is utilised by them as a source of energy. As regards its fate in the body, in fact, alcohol is strictly comparable to sugar, which is also an alcohol, though of a more complex nature than the substance under discussion. Like sugar, it is capable of supplying energy, which may be utilised in heat formation and mechanical work, and it may lead to the deposit of fat and to economy of the precious nitrogenous stores of the tissues. In fact, the more closely the metabolism under alcohol is examined, the more closely is it found to conform to that under an equivalent amount of carbohydrate, and it seems to me that the protagonists in the fight against

alcohol can only harm their cause by still refusing to accept these results. For the recognition that alcohol resembles sugars and fats in its fate in the tissues by no means implies that it is a suitable food in disease or in health. The same is true of vinegar and even of morphine under certain conditions. Before an oxidisable substance can be contemplated as a substitute, therefore, it must be shown that, given in quantities which have any significance in calories, it has no greater possibilities for harm than normal foods. Can alcohol be taken without toxic effects on the tissues in general, quite apart from those on the brain and more specialised organs? On this point experiment has shown that when alcohol is substituted for other forms of food in persons unaccustomed to its use, it sometimes fails to act as an equivalent for some days, during which the deficiency has to be made up by the combustion of other available sources of energy. This has been supposed to indicate some specific toxic action of alcohol on the tissues; but there are grounds for believing that alcohol does not stand alone in this relation, but that the same phenomenon occurs when other unaccustomed but unimpeachable forms of food are suddenly substituted for those which the tissues have hitherto consumed. In this point, then, alcohol appears to behave in the same way as other nitrogen-free foods.

But another series of investigations has shown that alcohol leaves the tissues in an impaired state in regard to the measures which the organism normally takes to protect itself from injuries either by living organisms or by poisons. No experiments were needed to show that the abuse of alcohol lessens the resistance to invasion by pathogenic organisms; the records of pneumonia in our hospitals and of cholera in the East indicate this beyond the shadow of a doubt. But these fail to show beyond question that the habitual use of alcohol in small quantities, or its therapeutic use, has this effect; and the whole interest of the question at present lies in the dietetic use of alcohol as contrasted with the drunkard's abuse of it. A number of animal experiments on the subject have been performed by inoculations of pathogenic bacteria, or of their toxines, before or after the administration of alcohol, the mortality being compared with that of animals inoculated in the same way but not treated with alcohol. In these the results have almost uniformly been arrayed against the use of alcohol, but,

unfortunately, the quantities of alcohol given scarcely correspond to the moderate use in man. Even Laitinen gave his rabbits about 1 c.c. per kg., which would correspond to about 4–5 oz. of whisky per day in a man. This quantity was insufficient to cause symptoms of intoxication in his animals, but the corresponding ratio could scarcely be considered within the limits of moderation in man.[1] Some recent work by Reid Hunt bears closely on this question, in that he finds that the continued administration of alcohol in small quantities renders mice and guinea-pigs much more susceptible to the effects of acetonitril, a poison which acts by the liberation of hydrocyanic acid in the tissues. Hunt considers his results due to alcohol deranging the metabolism in certain directions, notably tending towards an acceleration of some oxidative functions. And in this he sees a specific difference between alcohol and the carbohydrates, in that these have of course no such influence on the metabolic processes.

Hunt states that these changes arise from quantities of alcohol which correspond to that indulged in by "moderate drinkers," inasmuch as his animals showed no signs of intoxication. But a drop of alcohol per day for a mouse corresponds to an immoderate use in man; and in view of the importance of his evidence, it is extremely desirable that a more accurate determination of the amounts of alcohol given were available. For while I think there can be no question that alcohol in excess reduces the resistance of the general tissues to disease and may be deleterious to them in other ways, as Hunt's results indicate, it still remains undecided what is the lowest point in alcohol administration capable of inducing these effects.

On the whole, it must be conceded that small quantities of alcohol have not been proved to act deleteriously on the tissues in general, but, on the other hand, the threshold below which alcohol is innocuous has not been ascertained with accuracy, and probably lies nearer the limit of "moderate use" than is generally recognised.[2]

[1] Since this paper was written, a further series of experiments has been published by Laitinen, who finds that the prolonged administration to animals of quantities of alcohol corresponding to less than a glassful of whiskey or two glasses of port wine per day in man, exercise a distinctly deleterious action on the blood, and reduce the resistance to infection.

[2] In view of the statement made by Professor Reid Hunt during the discussion of this paper and the later publication by Laitinen just mentioned, I

The effects of alcohol on the central nervous system differ very considerably in different individuals. In the lower animals they are marked by depression, the symptoms being exactly similar to those of chloral or of the other narcotics. Occasionally, a transient excitation occurs, but this is due to the irritant action in the stomach, and is absent when more dilute solutions are administered, or when the alcohol is ingested in small repeated doses. In human beings the same depressant effect is often seen, the first symptoms being more or less drowsiness and heaviness, which subsequently pass into slumber. But in the majority of cases the first effects elicited are feelings of good fellowship, well-being, and liveliness, with increased confidence in the mental and physical powers. The face is flushed, the eyes bright, and the pulse and respiration are accelerated. Larger quantities lead to uncertainty and inco-ordination of the movements, shown in difficult and stammering speech and staggering gait, and still larger amounts induce sleep and narcosis, which may pass into complete anæsthesia, and eventually prove fatal. The symptoms of intoxication, therefore, appear to differ in the lower animals and in man, for while in the former there are generally no signs of excitement, in the latter this feature may be very marked in the beginning. And even in man the effects of alcohol offer marked contrasts in different individuals, and in the same individual at different times. For the excitement is very much more marked when drinking is indulged in in company with others, while when alcohol is taken with less exhilarating environments or in solitude, the excitement stage is very much less marked or may be entirely absent.

The effects of alcohol on the brain have been explained in two different ways : the view which appears at first sight to be the more natural one, is that it first stimulates the cerebral cells to greater activity and then depresses them ; that is, alcohol is believed to act on the cerebral grey matter in the same way as strychnine on the spinal cord. And this view, that alcohol is a central nervous stimulant, is still widely

feel that this paragraph requires modification. The very moderate use of alcohol (by which I mean the habitual daily consumption of one or two glasses of port, one or two pints of beer, or a glass of whiskey) appears from the researches of these authorities to induce definite deterioration of the tissues, and to render them more susceptible to attack by disease.

entertained both by the laity and by clinicians, while the majority of experimental observers rather lean to the view suggested by Schmiedeberg and supported by Bunge, Kraepelin, and many others, that the stimulation of the brain is only apparent. According to this theory, the excitement is caused, not by the augmented vitality of the nerve cells, but by a loss of the associations which ordinarily retard the expression of mental activity.[1] To adopt a mechanical simile, the brain may be compared to an engine fitted with powerful brakes. An acceleration of the motion may be due either to increased power of the engine (stimulation) or to the brakes being taken off, and it may be difficult for an onlooker to determine which is the true explanation. The apparent evidences of increased mental activity under alcohol, however, have proved for the most part illusory, when carefully investigated. The closer one approaches to the engine, the more evident it becomes that what appeared to be the result of increased power is really the effect of the removal of the brakes.

One argument against the stimulant action of alcohol is the narrow limits to which it is confined. All the recognised central nervous stimulants act on some particular part in small doses, but when larger amounts are ingested the stimulant action spreads over a wider area of the central nervous system, and gives rise to the symptoms characteristic of stimulation of that area. Caffeine, for example, first stimulates the mental functions apparently, but in larger quantities involves the motor sphere of the brain, and may finally stimulate the cells of the cord. Alcohol, on the other hand, appears to have only a depressant action on the nervous tissues, except in the human cerebrum. It is true that the exceptional development of the human brain might permit of a departure which is without analogy in other forms of poisoning.

But when the excitement stage is more closely investigated, it becomes apparent that all the cerebral functions are not facilitated by alcohol. It is common knowledge that under the influence of alcohol an individual may be more brilliant

[1] When it was propounded the rôle of inhibition in the central nervous system was not appreciated, or at any rate had not been experimentally demonstrated. The recent work of Sherrington has, however, shown that every movement involves motor and inhibitory impulses, and seems to give a firm basis for the depression theory of alcohol.

in conversation, more witty, more social, more generous in sentiment, but that he is not so careful in his statements, and has not that consideration for his own position or that of others which he ordinarily manifests.

The normal adult, in an environment which in a child would cause every symptom of exhilaration, maintains his self-control, partly because the position has lost its novelty, that is, he has associations which are wanting in the child, partly because the exuberance and gesticulations natural to the child are kept in check by his sense of the ridiculousness of these manifestations in later years. Remove the inhibiting associations, destroy the self-control of adult life, and the man becomes a child again in his sense of exhilaration and symptoms of excitement. The symptoms of intoxication which are ordinarily regarded as indicating stimulation of the brain do not necessarily involve this interpretation, but may be explained by a removal of those associations which ordinarily inhibit the external manifestations of emotion.

In a word, it is generally recognised that some of the highest functions of the brain are thrown out of action by alcohol administered in quantities which induce the phase of exhilaration. The further question is: What functions are actually increased in activity, and how far is this increase dependent upon the reduced activity of the processes which are depressed by alcohol?

Much valuable evidence as to the effect of alcohol on mental processes has been gathered in the psychological laboratories, especially by Kraepelin and his pupils, who have subjected the question to a large number of ingenious psychological tests. Thus it is found that typesetters do a smaller amount of work and make a much larger number of misprints when even a couple of glasses of beer are allowed, than when they perform their work without this drug. When a student was set to learn a number of meaningless syllables or a row of figures, he took a longer time to do so and made more errors in repeating them under alcohol than normally. Similarly, arithmetical calculations of all kinds were carried out much more slowly and with more errors, and the writing was slower and gave the impression of being that of an uneducated person who seldom had occasion to use his pen. Only in one respect was any increased aptitude shown—namely, in the transformation of

an idea into movement. And many ergographic experiments appear to show that small quantities of alcohol have the effect of temporarily increasing the capacity of doing muscular work, especially when the subject is fatigued. This augmentation is only transient, and the total work done in the course of the day is considerably reduced by alcohol, as has long been demonstrated in the case of forced marching. These might suggest the view that the motor cells are first put in a state of greater activity by the direct action of alcohol on them, but another explanation is equally applicable, namely, that an ordinary movement is hampered by a series of associations, and that when these are destroyed by alcohol the movement may be carried out more quickly. At the same time, the associations in ordinary life not only retard the movement but also restrict and direct it, and the result of their absence under alcohol is shown by the awkwardness and inaccuracy with which the movement is executed.

It is noteworthy that in these experiments those mental processes which were ordinarily performed readily were less retarded than others in which the subject was less practised and which required more effort. That is, the powers most recently acquired and most readily lost are those on which alcohol first acts, while those operations which have become habitual are less impaired. This is in complete accord with what is observed in the earlier stage of intoxication or exhilaration. The most recent acquisitions in adult life are the power of self-control and the feeling of self-respect, which are manifested in regard for the conventions of life, and in the prudence which leads one to avoid many procedures which in earlier life might have been indulged in without reproach. And under alcohol these are the first mental processes to be disordered. *In vino veritas*, in intoxication the natural man is exposed, stripped of the trammels of convention, and robbed of the fruits of experience and education.

Many other results of these experiments are of interest, but cannot be entered on here. One feature which bears a familiar aspect, and which was brought out clearly in many instances, is the confidence of the subject of the experiment that his efforts were unusually successful under alcohol, while the impartial record showed results far below the level attained during abstinence.

In all of these experiments the amount of alcohol taken was small, in no case sufficient to induce any of the more evident symptoms of intoxication. It is therefore of great interest to find in the later publications of Kraepelin's laboratory, that distinct impairment of the psychical powers was found to persist for a much longer time than would be anticipated; the average efficiency was not regained until from twelve to twenty-four hours had elapsed after the alcohol had been taken. If this proves to be true in the case of persons who have acquired a tolerance for alcohol, even moderate drinkers are never completely normal, their mental powers never recovering entirely from one dose of alcohol before the next is taken.

The results of these investigations on the mental state under alcohol, as well as many others which I have not discussed, appear to place the theory that alcohol acts as a narcotic upon a firm basis. I do not hold that it is absolutely determined, but some more satisfactory evidence must be brought forward in favour of the stimulation theory before it can be considered as a rival to that of Schmiedeberg. And this evidence must define what functions are stimulated, and must not be a repetition of the old statement, that the tone and vigour of the nervous system are maintained by alcohol.

But if the chief or even the whole action of alcohol on the brain were proved to be a narcotic one, this would not preclude its use in therapeutics. For here the chief object in the use of alcohol is not to induce but to repress cerebral activity, and the alleged stimulant action arises from a confusion of ideas; a similar confusion is met with in regard to opium, which was also regarded as possessing stimulant properties which recommended its use in acute diseases accompanied by cerebral symptoms. The result of both drugs is in reality cerebral depression, which manifests itself in a condition of euphoria. The disease often loses its strongest ally when the anxiety and worry of the patient are allayed by alcohol. He feels less concern and more resignation, not because his soul rises triumphant through the stimulant action of alcohol, but through his brain being less capable of dwelling on his disabilities, because it is partially narcotised.

Alcohol, therefore, is not to be regarded as exercising any unique action on the brain in disease, but resembles the other narcotics, and as a remedy must be compared with these. And

on the whole it emerges from the ordeal as not inferior in many points. Thus, none of them disturb the digestive tract less, and most of them exercise a more depressant effect on the centres in the medulla oblongata; for I think it may be taken as proved that in ordinary therapeutic doses alcohol does not depress the respiration, but, on the whole, tends to augment it even when no excitement is induced. Where a slight narcosis, sufficient to allay anxiety and induce rest is required, then, alcohol deserves consideration, but it is less certain in effecting a more marked depression, for which it cannot be compared with the modern narcotics.

The effects of alcohol on the circulation have long been a matter of dispute, many clinicians holding that in failure of the heart and vasomotor centre alcohol is of service, while others have found that it may be dispensed with. The experimental results have recently been discussed by Dixon, who suggests that alcohol may support the heart by acting as a food-stuff, and may thus increase the blood-pressure and improve the circulation. It is true that another observer has not been able to satisfy himself that alcohol acts as a food for the heart, but Dixon's results unquestionably re-open the question of the usefulness of alcohol in the treatment of acute circulatory failure, in regard to which a sceptical attitude has more recently been adopted by many of the leaders of the medical profession. And in addition to any direct action on the circulation, alcohol may prove of value in circulatory failure through its narcotic action in the same way as opium, over which it has the advantage of not inducing any embarrassment of the respiration.

To sum up, alcohol may be of some value in therapeutics as an adjuvant to foods, in order to render them more attractive, and thus improve their digestion, and also possesses some food value itself. It acts as a cerebral depressant, and may be useful in certain diseases in this way, and it may perhaps aid the failing heart. A small dose exercises no definite demonstrable poisonous effects on the tissues, and small repeated doses, though suspect, have not been shown to be deleterious.[1] If alcohol were a new synthetic remedy fresh from Germany, it might probably be hailed as a useful addition to therapeutics, but its popularity as a remedy would be short-lived. Not because of its failure

[1] But see footnote, p. 554.

to substantiate its claims as a narcotic, nor because it had proved fatal in the hands of physicians, but because an alcohol habit had been developed in some of the population. If one considers the few sporadic cases in which sulphonal or cocaine, for example, has given rise to a habit, and the discredit into which it has fallen in consequence, and compares the cases of disaster from alcohol met with every day, one cannot but feel that the drugs have been weighed in very unequal scales, and that any one who discards cocaine—undoubtedly a drug of great value—must, to be consistent, condemn the use of alcohol. This seems to me to be the ground on which we must take our stand. Alcohol is a drug which may be useful in therapeutics, although I think it can hardly be considered indispensable, but which has so often given rise to habit that its use must be curtailed to the utmost limit. In some conditions, as in old age and debility, it may be justifiable to neglect its drawbacks, exactly as in some forms of malignant disease the patient may be allowed to contract the morphine habit; but let us at any rate advise it here with eyes open to the risks run, and with the recognition that we are prescribing a drug and not merely a placebo. It may be argued that alcoholism has almost never arisen from the therapeutic use of the drug, and it is true that the responsibility for alcoholism does not rest upon the medical profession in the same way as that for morphinism or cocainism. But the public are justified in regarding alcohol not as a drug, but as an article of diet, as long as the physicians order it in the casual way which is familiar to all of us. How often is alcohol not ordered but allowed by the medical man at the suggestion of the patient, and how many physicians allow it, not believing that it will do any good, but assuming that it will do no harm, and even not hesitating to make the statement! The laity can hardly be blamed for ignoring the evidences of danger presented daily in their streets, if their scientific mentors themselves adopt this ambiguous position, and the medical profession cannot complain if they are accused of indifference towards the greatest evil of their country and their age.

THE THEORY OF DIABOLO

By C. V. BOYS, F.R.S.

It would be an interesting subject for a course of lectures or a series of articles to trace the effects of rotation in balls and other objects used in games and in other pursuits. Some of these are fairly obvious, as, for instance, the effect of a spin on a cricket-ball causing it to break after contact with the ground, or the effect of a screw in billiards, where the ball has a rotation about an inclined axis and bounces from the cushion at an angle which by no means obeys the laws of reflection. Here also, in consequence of the rotation the height of the cushion has to be seven-tenths of the diameter of the ball, for in the case of pure rolling the upper part of the ball may be considered to be travelling more quickly than the lower part, and so, if the cushion were only the height of the centre the upper part of the ball would go on and take the rest of the ball with it. Less simple than these are the effects of the air in causing a spinning ball to veer away from the course that it would take if it did not spin. The best known of these is that shown by the flight of a golf-ball, which was first carefully investigated by the late Professor Tait. When the ball is fairly struck by the club, the front face of which slopes somewhat backwards, it is struck at a point below its centre. The rotation imparted is in such a direction as to cause the lower part to move forward most quickly and the front part to move upward. At one time it was supposed, and I believe clearly proved in the armchair in an analogous case, that the front portion moving upward would cause the ball to roll, as it were, upon the air compressed in front of it, and so cause a departure from the natural trajectory, which in the case of the golf-ball would be downwards. As every one knows, the exact reverse is the case, and a proper consideration of the action shows that it should be so, for the air-pressure can be shown, both by theory and by experiment, to be greater below a ball spinning and moving in the directions followed by a golf-ball than above. Professor Tait established

the fact that upward forces due to this cause may be set up which are two or three times as great as the weight of the ball. Another example of this, but less easily followed, is the flight of a spherical bullet from a bent smooth-bore barrel. If such a barrel is curved in a horizontal plane so as to be suitable, according to the story of our childhood, for shooting any one round a haystack, the bullet, far from continuing the curve which it was compelled to follow in the barrel, acquires therein a spin, owing to its rolling along on the concave side, and this spin produces a curvature when free opposite in kind to that of the barrel that gave the rotation. Such a curved flight of a ball is well known in games; the light ball of lawn-tennis when well cut follows a markedly curved course, and, best of all, the child's india-rubber air-ball or balloon when cut by a sweeping stroke of the hand curves rapidly upwards in its flight and provides the material for an excellent and violent indoor winter game.

Mysterious as some of these air-effects may be, they are wholly eclipsed by the queer and apparently semi-contradictory effects of the rotation of a body which are noticed when anything is done to twist the axis of rotation into some other direction. If a grown-up and otherwise well-educated man had never seen a top spin, and, being familiar with the fact that such a body will not stand up upon its point when not spinning, and with the whole science of statics, were suddenly presented with the phenomenon of a spinning-top it is difficult to realise, familiar as we are with the result from our earliest childhood, how great would be his surprise. The fact that it should stand up at all would seem sufficiently uncanny, but its gentle gyrations round the upright position, more rapid as the rate of spin diminishes, would seem to defy explanation. It is only universal familiarity with the phenomenon that prevents surprise or any anxiety in the majority of people to dissolve the mystery. It would be out of place in an article such as this to prove from the simple laws of motion propounded by Newton that a top should spin as it does, or, more generally, how any spinning body will behave when any forces are applied to it which would, if it were not spinning, move the axis about which it happens to be turning into some different direction. This subject is treated in a charming manner by Professor Perry in his book on *Spinning-Tops* and by Professor Worthington in his *Dynamics of Rotation*,

and with rigid accuracy by Professor Greenhill in his articles in the *Encyclopædia Britannica*. It is sufficient here to state shortly the facts. Take the case of the spinning-top. This, if not spinning, would fall over, the toppling-over effect of gravity being greater as the inclination is greater. When the top is spinning the forces due to gravity are the same as before, tending to drag the axis of spin over and downwards, but in consequence of the spin it has a different effect: the axis does not move downwards but sideways, always at right angles to the direction in which it is urged, and so the top gyrates. Further, the rate of moving sideways is greater as the rate of spin is less. If the point on which the top spins is adjustable so that it may be made to project more or less, or may be withdrawn until it is above the centre of gravity, then as it is fixed nearer to the centre of gravity the toppling effect of gravity will be less and the top will gyrate more slowly. When the point on which it spins is at the centre of gravity the toppling effect of gravity is destroyed, and so it ceases to gyrate, and when the point is raised higher still gravity tends to topple no more, but to set it upright: it then gyrates the other way. When gravity acts so as to make it fall it gyrates in the same direction as it spins; when gravity acts so as to set it upright it gyrates in the opposite direction. An example of a slow gyration of this sort is presented by the earth, which would, if it were spherical, maintain the direction of its axis of rotation indefinitely. Any star in the line of this axis would be for all time the pole star. Both the sun and moon in their attraction upon the "equatorial protuberance," or excess of matter outside the sphere, act in such a manner as to drag it towards the plane of the ecliptic, or the earth's orbit round the sun. If this is looked upon as a level, then the sun and moon act together so as to set the top upright. The gyrations then are in the opposite direction to the spin, which is also the direction of revolution round the sun, and so the "equinoxes precess." The pole of the earth describes a circle round the pole of the ecliptic once in about twenty-six thousand years.

When a spinning body of other shape than a ball is projected through the air, the effects of the air upon the direction of the axis of spin, and hence on the motion of the body, give rise to numerous interesting problems. For instance, a disc spun and thrown by the right hand edgeways turns so that the right side

of it rises and it veers to the left; on the other hand, a boomerang started with the same motion rises and comes back again. An elongated bullet neither follows the trajectory, like an arrow, nor maintains the direction of its axis, but conically screws itself round a line slightly above the trajectory. Whenever a spinning body is projected through the air which is in any respect different in its conditions from other cases which have been investigated, a new problem is almost certain to be found, and it is not safe to jump to conclusions.

In the case of the diabolo spool there are really no difficulties, because the air-effects are barely noticeable, and they are of the simple kind observed with golf-balls, tending to deflect the spool to the right as it falls if it is spinning rapidly with a right-hand spin. Ordinarily, in the draughty and eddying enclosures called gardens attached to houses in London, this deviation from a straight fall is not easy to detect, and it certainly is of no importance in the game. If, however, the spool were much lighter, and were ribbed or roughened like a golf-ball, the air-effect would be increased.

With an ordinary spool, the form of which it is unnecessary to define, the centre of gravity is above the string support. It is therefore unstable, and on whichever side it happens to incline, on that side, if not spinning, it will fall. Gravity acts in such a manner as to topple the axis of spin over towards a vertical direction. With the usual right-hand spin the hands are moved in such manner that the string is jerked tight when the right hand is rising, and is loose when it is falling, and the spool gets its support mainly while the string under it is moving from left to right. The upper part, therefore, moves from right to left. In order to correct the level of the axis, when for any reason this ceases to be level, it is necessary to apply forces twisting it not in the desired direction, but in a direction at right angles thereto. Any child will tell you to put the left hand forward if the far end is drooping. Putting the left hand forward means the application of a twist on the axis, tending to turn the far end to the right. This may be proved in a moment by placing the spool on the ground with the string under it and then gradually lifting it with the left hand forward. It will then, not being in a condition of spin, immediately turn so that the far end moves to the right. If the left hand is put forward when the spool is spinning, the effect of the tendency to twist

to the right is a movement in a direction at right angles to the tendency, and the far end rises. There are two directions at right angles to this tendency, one upward and one downward. It is puzzling sometimes to know which right angle will be followed. In the present case it is easy to tell by reference to the known movement of a top. Consider the axis of the spool to be the axis of the top and the far end to be the support of the top, or point on which it is spinning in an anti-clockwise direction, the direction of gravity being supposed for the moment away from you. The action of the string tending to turn the far end to the right or the near end to the left corresponds to the action of gravity on the top when it is leaning to the left, tending to make it fall more to the left. It does not do so, but moves sideways in the direction of the spin, *i.e.* actually towards the earth; or, in other words, the other end, or far end, is raised. If the spin is left-handed of course the result is reversed, and so it is a pity when learning and acquiring the habit to base it upon a consideration which must be reversed when the direction of spin is reversed. The better instruction to follow is to jerk the business hand toward the high side—it being understood, of course, that the business hand is the one which, by its upward jerk, imparts the spin. With such a rule as the early guide the instinct, which is quicker than the recollection and application of any rule, is from the first directed aright, and no conscious effort of reversal is needed whether the direction of spin is right or left handed or the near or the far end is falling.

In order not to be tied to the crab-like method of playing sideways, which is so often seen, it is well to practise playing with a right or left spin indifferently. If playing alone, the change may be brought about by moving round to the side of the spool which is moving upwards and catching the spool on the stick held by the passive hand, then in running the spool down on to the string it will be found to be reversed in direction as seen by the player, but not as regards the points of the compass. This catching on the passive stick is more easily effected, at first, at any rate, by catching on the active stick first and then catching it on the passive stick. The direction of spin may also be reversed by throwing the spool up and turning half round before catching it on the string. Quite a moderate amount of practice, reversing every time by one or

other method, makes the direction of spin a matter of perfect indifference.

I have already referred to the fact that it is necessary for the player to make a half-turn if he would face the spool between every reversal. This is merely another way of saying that the spool maintains its direction in space—that is, it does so if it is perfectly balanced. It is impossible in that case, and provided that it is kept level, to get the spool to veer round to any appreciable extent. If the disturbances were a good deal less than they are, it would in this country appear to follow the sun, but at the reduced rate of nearly 12° per hour, in consequence of the rotation of the earth. Though such accuracy is beyond practical attainment, the persistence of direction is very marked. If while spinning the diabolo a person walks round the garden, he will soon find he is getting his arms involved with one another, as the spool will not turn and the sticks must not either. Or if while travelling in the railway along a curve a passenger is spinning a diabolo and maintaining it level, the apparent turning of the spool will indicate the actual turning of the carriage in the opposite direction. A good place to try this is in the "Bakerloo" tube where it enters the Regent's Park in its northward journey, or in the Hampstead tube in the Euston district.

I have insisted upon the necessity of keeping the spool level when making this experiment. Suppose, for instance, that the far end is down a little and that the usual right-hand spin is being applied, then, as the far end is down to a certain extent, the centre of gravity, instead of being above the string, is on the far side of this position, and gravity tends to topple the spool over on the far side—*i.e.* to turn the spinning axis so that the far end moves downwards. Just as the tendency of the string support to turn the far end to the right makes it actually rise, as already explained, so this tendency of gravity to make the far end move downwards causes it, in consequence of its rotation, to go sideways, and the particular sideways in this case is to the right. If, then, a player desires to work the spool round he has merely, by thrusting one hand forward, to make one end dip somewhat, and then to keep spinning it in that position, when it will veer round—more quickly if the spin is slow—and then, when it has the required direction, to bring the low end up again by drawing the same hand towards himself. It does not matter whether the spin is right or left handed; if the right hand

is put forward to cause one end to dip, the spool will then veer to the right, and *vice versa*, for the end that dips is reversed with a reversed direction of spin, and the action of the reversed tendency to fall, combined with the reversal of spin, gives the same direction of veering. This process was described by a speaker at the Physical Society at a recent meeting where I was showing a peculiar spool, to which I shall next refer.

An ordinary fly-wheel or a disc is twice as effective as a fly-wheel if it is mounted to spin in its own plane, as it would be if it were made to spin on one diameter as an axis. Its moment of inertia is said to be twice as great when spinning as it does in practice as it would be if made to spin about a transverse axis. On the other hand, a diabolo spool or an elongated bullet is less effective as a fly-wheel when spinning about its axis of rotational symmetry. In these cases the moment of inertia is a minimum, while in the former it was a maximum when spinning in the usual manner. Anything, whatever shape it may have, must have some direction about which the moment of inertia is a maximum or a minimum, and it may have a single transverse axis about which it is correspondingly a minimum or a maximum.

If any body is set spinning about any axis and then liberated, it will continue to spin about that axis and resist disturbance only if the axis of spin is one of maximum or minimum moment of inertia. If the body were spun about any inclined axis and liberated, then, according to the position in the body of the inclined axis and the relative values of the maximum and minimum moments of inertia, the axis about which it thereafter is momentarily spinning will move within the body according to one curve and in space according to another, for which an explanation must be sought in Maxwell's Collected Works, vol. i. p. 248. If, on the other hand, the spinning body were a uniform sphere, in which the moments of inertia about all diametrical axes are alike, it would have no tendency to move the axis of spin in any particular manner within itself, and any disturbance would set this axis wandering in the sphere, or, as Maxwell put it, the sphere has no dynamical backbone.

It is not necessary in order that a thing should have equal moments of inertia in all directions that it should be spherical in shape. A long round thing has a minimum moment of inertia

about its axis of symmetry, while a flat round thing has a maximum moment of inertia about this axis. A bullet or an ordinary diabolo spool is an instance of the former, while a fly-wheel or a disc is an instance of the latter. A diabolo spool need not have the usual angle of about 70°, it may be made longer or wider. As it is made wider the moments of inertia in the two directions become gradually more alike, and if it were made wide enough it would correspond in this sense to a fly-wheel, and the respective values would be inverted. There must be, therefore, some intermediate width or angle of cone which makes the moments of inertia in all directions the same, so that dynamically it is the same as a sphere.

It is easy to prove that in the case of a thin hollow double cone, with the ends open and joined point to point, the proportion which gives the spherical characteristic is reached when the angle of the cone is nearly 110°, or when the tangent of the semi-vertical angle is $\sqrt{2}$. All matter added to such an ideal skeleton, without it equatorially makes the axis of rotational symmetry an axis of maximum moment of inertia, all added beyond in the direction of the axis makes this a minimum. A judicious addition of matter without and beyond leaves the double cone dynamically the same as a sphere. If, then, a spool is made of this angle, and of such a thickness as to give a convenient neck for the string by addition of matter without the ideal cone, and by the addition of about the same amount beyond the ideal cone, the resulting spool will be dynamically very nearly a sphere. It is best to make it with an axial hole and with a very slight preponderance of matter without the ideal cone. The moment of inertia about the axis of spin is then just a maximum, and the spool spins perfectly. A number of sticks may then be made of different lengths and thrust centrally, one at a time, into the hole. If any one of these is so exactly chosen in length as to make the moments of inertia in all directions the same, then spinning becomes impossible for the reasons given. In order to ascertain if any stick is too long or too short it is merely necessary to suspend the combination from a torsion wire so as to oscillate about the axis of rotational symmetry and about a transverse axis successively. Then if the time of oscillation about the former is the greater, the stick is too short, and *vice versa*. In order to make spinning really hopeless the time of oscillation should not differ by anything

like so much as 1 per cent., but when equality to this extent is reached the spool becomes sufficiently unmanageable.

When a stick has been properly adjusted the equality fails if the stick is not centrally placed, and the spool can be spun again quite easily. Now, however, being out of balance, the heavy end in tending to fall actually goes sideways, and more quickly so at starting, when the spinning is slow. With a right-hand spin the heavy end, whichever way it is pointing, veers to the right. This may, of course, be equally well shown with any spool which is unbalanced, or which is made so by attaching a nail or a lump of wax to one end. A stick too short to give the spherical property when centrally placed may, nevertheless, do this when pushed out of centre, and then, though the combination will spin perfectly in the first position it is impossible in the second.

It might be thought that the ball in the game cup-and-ball, which at least is a sphere in fact, should not maintain its axis when spun with a view of being caught on the point. But here there are two answers. The first is that though outwardly a sphere the axial hole made for the point to enter destroys its spherical properties. This may be the case to the extent of an inequality in the moments of inertia of perhaps as much as 5 per cent., and this is quite enough to give stability. I have, however, turned a groove in the equator of a well-made ball of this kind to such an extent as to bring the moments of inertia the same, at least to a small fraction of 1 per cent. I was rather surprised to find that I caught this sophisticated ball the first time I tried it. The case, however, is not parallel with the diabolo spool in this respect. While the tweaking of the string on the spool is certain not to be exactly symmetrical and free from disturbing influences, the axial string from which the ball is suspended lifts it when spinning with a pull which must be as truly axial as the turned work is round, and so the disturbance, if any, must be so slight that the ball, in the short time that it is free, has no time to take up an appreciably different position before it is caught. All the time that it is on the string it is held true, while, on the other hand, the spool is only supported and tweaked by the string a very small fraction of the whole time.

Of all the appliances in the class-room for illustrating the precessional properties of rotating bodies I do not know one

which is so inexpensive, simple, and handy as the now popular diabolo. It is whispered that mathematical professors do not always illustrate what they wish very successfully when using gyrostats and Maxwell and other tops. The diabolo seems to have been invented for their special benefit. A complete and proper demonstration of the points described above, and of many others, no doubt, would add enormously to the joy of the class. If at any time the spool should prove refractory the expositor could fall back upon the convenient formula $\tan \theta = \sqrt{2}$, which in time might be contracted to tan, and would so serve the double purpose of an explanation and a harmless but comforting expletive. As a game I do not at all feel inclined to agree with the view that it is not worth while, that it is silly, that it is a mere passing craze. It may, and no doubt will, go out of fashion as quickly as it came in, if indeed it has not already done so, but that is not the fault of the game but of society, who equally threw over cycling before the motor car had destroyed that invigorating pursuit.

SYNTHETICAL DRUGS

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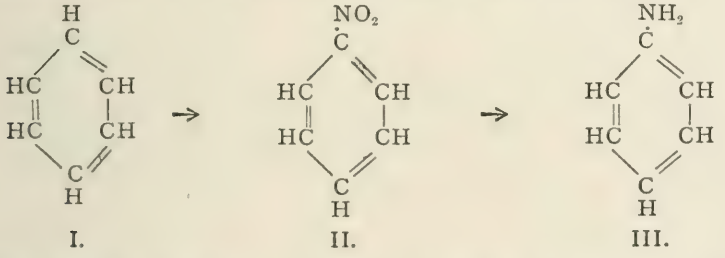
The medicaments falling into the category of synthetical drugs are those which are built up by chemical means from simpler carbon compounds, and not extracted ready-formed from products of the vital activities of plants or animals. In this article it is intended to discuss in simple terms the chemical nature of a typical selection of these therapeutic agents, the trivial or commercial names of which are often household terms.

In 1906 chemists from all parts of the world gathered together in England to celebrate the jubilee of the coal-tar industry, the fiftieth anniversary of the discovery of the colouring matter, mauveine, by the late Sir William Perkin, and 1906 may also be regarded as the jubilee year of the synthetical drugs, for it was in an attempt to synthesise from aniline the valuable alkaloid, quinine, that Perkin discovered mauveine, his researches on aniline being the pioneers of other investigations which led to the employment of this remarkable base, aniline, in the production of compounds of therapeutic value. It is therefore, at the outset, necessary to consider, even though very briefly, the chemistry of aniline and its parent hydrocarbon, benzene. The latter substance, discovered by Faraday in 1825, is the chief constituent of the volatile oil obtained on distilling ordinary coal tar. Chemical analysis shows that the compound consists of twelve parts of carbon united with one part of hydrogen or, in the language of the atomic theory, one atom of carbon combined with one atom of hydrogen. Furthermore, a consideration of its vapour density and other physical properties indicates that a molecule of this hydrocarbon—that is, its smallest conceivable part—is somewhat complex and contains no less than six of these pairs of atoms. A general survey of the compounds of carbon shows that this element possesses in a marked degree the property of accumu-

lating in the molecules of these substances. In certain organic compounds the carbon atoms are arranged in chains which are either straight or branching. If we consider one of these chains having six carbon atoms, and if we suppose further that the chain is coiled so that the ends meet like a snake with its tail in its mouth, we then get a representation of the carbon backbone of the benzene molecule. To each of these carbon vertebræ one of the hydrogen atoms is attached; and now to give the finishing touch to our benzene ring we must consider what is the usual habit of combination of carbon in the many substances in which it is present. Of the thousands of carbon compounds known there are scarcely any which furnish exceptions to the general rule that this element is quadrivalent, or in other words that its atom has four bonds or valencies with which to attach itself to other atoms.

The following graphical formula I. for benzene indicates one of several ways in which this condition is satisfied, this particular mode of representation being due to Kekulé:



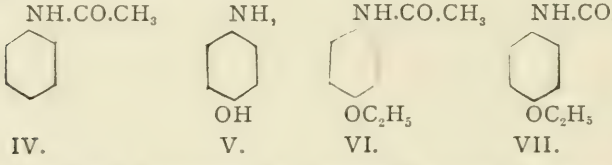
I. II. III.

The double linkings represent points of great reactivity in the molecule, and their presence exerts a very profound influence on the chemical properties of benzene and its derivatives. It is, moreover, largely owing to these double linkings that benzene derivatives are so frequently of therapeutic importance. The physiological action of benzene itself is, however, only slight, the compound having merely the depressing hypnotic effect characteristic of the hydrocarbons in general.

Antipyretics

Aniline (formula III.) is derived from benzene by first treating the hydrocarbon with nitric acid whereby nitrobenzene (formula II.) is produced and then replacing the oxygen atoms in the latter compound by two hydrogen atoms. This process is

called reduction, and is carried out very simply on a large scale by heating the nitrobenzene with iron filings suspended in slightly acidified water. Aniline resembles ammonia in some of its properties, for it is a base capable of yielding well crystallised salts such as aniline hydrochloride and sulphate. Both the base and its salts have a marked physiological action, and in fact they are powerful poisons. These substances have a beneficial effect in lowering the temperature and subduing pain, but on the other hand they have a very deleterious action on the red corpuscles of the blood, bringing about a destruction of the hæmoglobin. Aniline poisoning is characterised by the blue appearance of lips and nails, failure of respiration, giddiness, coma, and finally death. These acute symptoms are, however, considerably diminished by converting aniline into its acetyl derivative, acetanilide, a substance which has been employed as an antipyretic under the name of *antifebrin*[1] (formula IV.). This compound is readily prepared by heating together aniline and glacial acetic acid: $C_6H_5NH_2$, $CH_3 . CO_2H - H_2O = C_6H_5 . NH . CO . CH_3$.

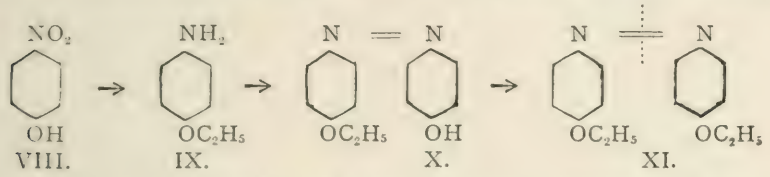


IV. V. VI. VII.

It should, however, be borne in mind that the acetyl group $CO . CH_3$ is readily removed within the tissues either by hydrolysis or oxidation, so that aniline is regenerated, and its poisonous effect is produced only in a less acute form than when the base itself is administered. The continued exhibition of antifebrin is to be deprecated as likely in the long run to produce aniline poisoning. It has been found that aniline is converted in the system into para-aminophenol (formula V.), which is then eliminated in combination either with sulphuric acid or glycuronic acid $COH . [CH . OH]_4 . CO_2H$. This action of the organism in converting aniline into the less poisonous para-aminophenol has been taken into account in the production of the antipyretics of the phenacetin series.

[1] The full graphical representation of the benzene ring or nucleus in formulæ I. to III. has now been simplified to the hexagon represented in formulæ IV., V., etc. It will be seen that this benzene nucleus is present in the majority of the synthetical drugs discussed in this article.

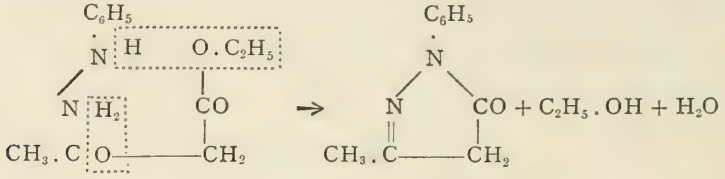
Phenacetin itself (formula VI.) is a febrifuge and an analgesic which is conveniently prepared by the following series of operations: Para-nitrophenol (VIII.) obtained as one of the products of the action of nitric acid on phenol (carbolic acid) is converted by treatment with ethyl sulphate (ethylation) into nitrophenetole $NO_2.C_6H_4.O.C_2H_5$, and this substance is reduced to phenetidine (IX.). This base when treated in succes-



sion with nitrous acid and an alkaline solution of phenol yields the complex compound (X), which is then ethylated to form the substance XI. It will now be noticed that the product XI. is symmetrical about the dotted line, and when it is reduced with tin and hydrochloric acid it splits into two parts at this point, each half taking up two hydrogen atoms and giving rise to a molecule of phenetidine (IX.). One molecule of phenetidine is made to undergo the series of changes represented by X. and XI., while the other molecule is acetylated and thus converted into phenacetin (VII.). This mode of procedure is adopted because of the difficulty of preparing pure paranitrophenol, and in this way an initially small amount of paranitrophenol can be made to produce a large quantity of phenacetin. This drug is somewhat sparingly soluble in cold water, but when the acetyl group is replaced by the lactyl group $CO.CH(OH).CH_3$ derived from lactic acid a more soluble compound is produced to which the name *lactophenin* (formula VII.) is given. This substance has an antineuralgic action; its lactyl group is more readily split off than the acetyl group of phenacetin, and this change occurs under the influence of the acid gastric juices, whereas phenacetin, *methacetin* $NH(CO.CH_3).C_6H_4.OCH_3$, *triphenin*, and other substances of this series are hydrolysed only by the alkaline juices of the intestine.

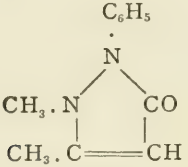
Antipyrine, one of the most important drugs of this group, was originally discovered by Knorr in 1883 in an investigation on the condensation of phenylhydrazine, $C_6H_5.NH.NH_2$, and ethyl acetoacetate, $CH_3CO.CH_2.CO_2C_2H_5$. These two substances, the former of which is an aniline derivative whilst the

latter may be regarded as a complex substance of the acetic acid series, interact to give rise to a compound containing a new ring in the manner indicated in the following diagram:

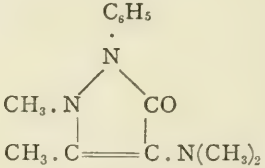


XII.

This product, phenylmethylpyrazolone (XII.), is physiologically inert, but on methylation (treatment with methyl iodide) it gives rise to phenyldimethylpyrazolone (XIII.) or antipyrine.



XIII.



XIV.

This compound is a valuable antipyretic and antineuralgic; it reduces febrile temperatures to the normal, and the subsequent rise of temperature is gradual and unaccompanied by shivering fits. The reduction of temperature is maintained for eight to twenty hours.

Knorr's good fortune in synthesising a therapeutic agent of this order is gauged by the fact that although many other derivatives of the pyrazolone series have been prepared and patented as antipyretics, only one has shown itself to be of anything like the same value as antipyrine. The drug in question is the substance *pyramidon*, which has been placed on the market by the firm of Meister, Lucius & Brüning, who were also the first to prepare Knorr's antipyrine on a manufacturing scale. Pyramidon, dimethylamino-antipyrine (formula XIV.) is prepared by treating antipyrine with nitrous acid, reducing the resulting nitroso-antipyrine to amino-antipyrine and then finally methylating this base to obtain the required compound. This drug is thrice as active as antipyrine; its action begins more gradually and continues for a much longer time. It is prescribed in rheumatism, influenza, and typhoid fever; it forms salts with

the acids of which the most important therapeutically are the salicylate and bicamphorate.

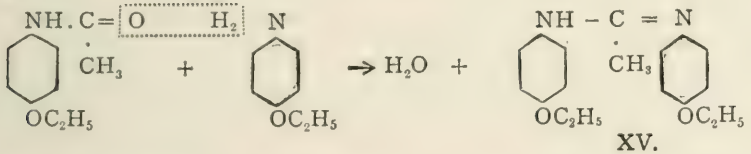
Migrainine, another drug of this series, is antipyrine-caffeine citrate; it is indicated in influenza, neuralgia, and insomnia.

Trigemine (M., L. & B.) is an additive product of pyramidon and butylchloral hydrate $CCl_3 . CH_2 . CH_2 . CH(OH)_2$ which has a marked analgesic action.

Anæsthetics

Closely allied chemically to the phenacetin series are some of the cocaine substitutes employed to produce local anæsthesia.

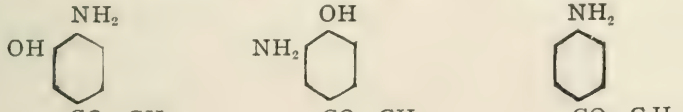
Holocaine is the hydrochloride of the base XV. produced by condensing phenacetin and phenetidine, $C_2H_5O . C_6H_4 . NH_2$. in the presence of phosphorus oxychloride, an agent which serves to remove a molecule of water in the manner indicated below



XV.

As an anæsthetic for operations on the eye its effect is prompt and lasting, and is not accompanied by mydriasis or disturbance of the accommodation of vision. On account of its toxic properties holocaine is not adapted for hypodermic use.

Orthoform (XVI.) and *new orthoform* (XVII.) are the names applied to two isomeric bases the latter of which is generally

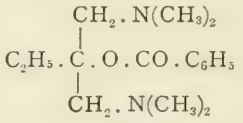


XVI. XVII. XVIII.

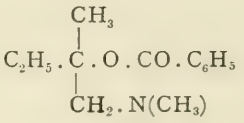
employed at present owing to its lower price. Like cocaine, these compounds render insensitive the nerve-endings and nerve-trunks with which they come into direct contact. This local anæsthesia is, however, not produced through the unbroken skin. A similar substance, *Anæsthesine*, ethyl para-aminobenzoate (XVIII.) is also employed as a local anæsthetic, and is non-irritant and non-toxic. The three foregoing compounds have been placed on the market by Messrs. Meister, Lucius & Brüning.

Novocaine, a derivative of anæsthesine having the formula $NH_2 . C_6H_4 . CO_2 . C_2H_4 . N(C_2H_5)_2$, HCl, is a powerful local non-irritant anæsthetic, seven times less toxic than cocaine, but somewhat transient in its effects.

Alypine, a local anæsthetic recently put forward by the Bayer Company, is the hydrochloride of tetramethyldiaminodimethyl-ethylcarbinyl benzoate (XIX.).



XIX.



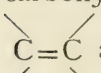
XX.

This drug has the useful properties of cocaine without its disadvantages, as even in large doses it does not injuriously affect the heart or respiration, and moreover it does not produce mydriasis.

Stovaine is the hydrochloride of a similar base (XX.); it is produced in the so-called Grignard reaction by the interaction of magnesium ethyl bromide and dimethylamino-acetone followed by benzoylation of the product.

Hypnotics

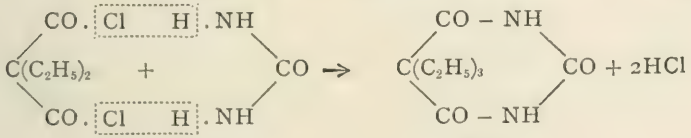
It has already been pointed out that the hydrocarbons themselves have slight hypnotic properties, which, however, become more pronounced when hydroxyl (OH) is introduced into the molecule. This increase in physiological activity is not, however, due to any narcotic action of hydroxyl, which on the contrary has a stimulating tendency. The opposing tendencies of the hydrocarbon and hydroxyl groups are illustrated by the well-known physiological action of ethyl alcohol. Morphine, again, owes its therapeutic action to the presence in its molecule of two hydroxyls, for when these are replaced by methoxyl or ethoxyl the narcotic properties of the alkaloid disappear.

In this connection the hydroxyl must be regarded as an unsaturated group owing to the presence of bivalent oxygen, and the physiological function of these unsaturated groups (hydroxyl, carbonyl, CO, and the doubly and trebly linked carbon atoms  and $-C\equiv C-$) is to furnish points of attachment between the drug and the reacting compounds of the protoplasm.

The synthetical hypnotics fall into three groups: (1) those containing halogens; (2) those containing alkyl groups and particularly the ethyl group; (3) those containing aldehydic or ketonic groups. Some hypnotics owe their soporific properties to a combination of these characteristics.

Isopral (trichloro*iso*propyl alcohol) is an example of an alcohol containing chlorine, recommended by the Bayer Company as a substitute for chloral hydrate. Isopral is more efficient than chloral and is freer from the depressing effects of the latter. Moreover, it is devoid of any cumulative action or unpleasant after-effects.

Diethylbarbituric acid (XXI), also known as *veronal*, may be regarded as an example of a hypnotic containing alkyl groups. It may be produced by condensing urea (carbamide) with either diethylmalonyl chloride or ethyl diethylmalonate, and many other methods of preparation are being patented even at the present time. Veronal is a colourless inodorous crystalline

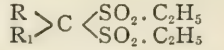


XXI.

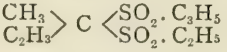
powder melting at 191°C, and dissolving in 12 parts of boiling and in 145 parts of cold water. It is a very satisfactory hypnotic and sedative, rapid in its action and free from untoward sequelæ; it has no disturbing effect on the heart or respiration. Fischer and Mering, who discovered veronal, have since suggested the employment of dipropylbarbituric acid under the name of *proponal*. This substance is also very rapid in its action, doses of 0·2 gram inducing sleep in from fifteen to forty minutes.

Hedonal is a compound of comparatively simple structure $\begin{matrix}CH_3\\C_3H_7\end{matrix}\!\!>\!CH\,.\,O\,.\,CO\,.\,NH_2$ which is advocated by the Bayer Company as a safe soporific. Experiments have shown that this compound is completely oxidised in the system to water and carbonic acid, and it is accordingly quite devoid of any cumulative action. It is indicated in cases of sleeplessness due to mental strain or occurring in the course of neurasthenia or hysteria. When a prolonged use of hypnotics is required it serves as a useful alternative to the other soporifics.

There is an interesting class of hypnotics containing sulphur which illustrate the influence of the ethyl group in the development of the soporific effect. They are produced by the condensation of ethyl mercaptan, $C_2H_5.SH$, with a ketone, $RR^1:C:O$, whereby a mercaptol, $RR^1:C(S.C_2H_5)_2$, is produced, which is then oxidised to a disulphone XXII.



XXII.

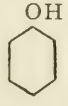


XXIII.

When acetone $(CH_3)_2C:O$ is employed in the condensation, *sulphonal* $(CH_3)_2C(SO_2.C_2H_5)_2$ is ultimately obtained; when diethyl ketone is used, *tetronal* $(C_2H_5)_2C(SO_2.C_2H_5)_2$ is the final product, whilst methyl ethyl ketone leads to the production of *trional* (Bayer). The hypnotic action increases with the number of ethyl groups, tetronal having the strongest narcotic effect. Trional, the intermediate member of the series, is, however, most often employed.

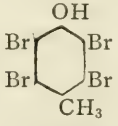
Antiseptics and Astringents

In considering the febrifuges, aniline was taken as the starting-point, and, in a discussion of antiseptics, phenol (carbolic acid, XXIV.) may be regarded as the prototype.

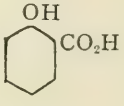


XXIV.

XXV.



XXVI.



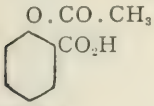
XXVII.

Phenol was, in fact, the first antiseptic recommended in surgical practice when it was employed in the original method of operation introduced by Lister. Although free from the destructive action exerted by aniline on the red corpuscles, phenol is a powerful irritant, and can only be administered internally in very small doses; in larger amounts it has a paralysing effect on the motor nerve-endings. The introduction of a methyl group into the nucleus as in para-cresol (XXV.) brings about a diminution in the poisonous character of phenol and at the same time increases the germicidal power of the substance. On this account the isomeric cresols (para-, meta-, and ortho-) are extensively used in disinfectants of the *lysol* type. The further substitution of halogen atoms for the

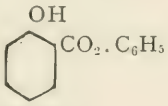
hydrogen atoms of the benzene nucleus also greatly increases the germicidal efficacy of phenol and the cresols. Tetrabromo-para-cresol (XXVI.) and tetrabromo-ortho-cresol are among the most powerful of known germicides.

It has generally been found that the introduction of the acidic groups, carboxyl, CO_2H, and sulphonyl, SO_3H, diminishes very markedly the toxic action of a drug. Benzoic acid, $C_6H_5.CO_2H$, for example, is a substance producing only a very slight physiological effect. When a carboxyl group is introduced into the phenol molecule in a position contiguous to the hydroxyl group *salicylic acid* (XXVII.) is obtained. This product, in the form of its sodium salt, is a very important drug; it has a powerful antiseptic and germicidal effect, is free from the caustic property exhibited by phenol, and it has, moreover, a specific action in acute rheumatism. In its internal effect it greatly resembles quinine, even to the extent of producing a ringing in the ears and transient deafness. When there is toleration of the drug the exhibition of salicylic acid gives excellent results in the treatment of rheumatic troubles, but in certain cases the acid is apt to produce gastric disturbances, and to overcome this unpleasant effect various derivatives of salicylic acid have been put forward.

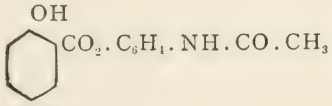
The well-known drug *aspirin*, acetylsalicylic acid (XXVIII.), is a good example of this series.



XXVIII.



XXIX.



XXX.

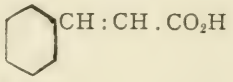
Owing to its insolubility in the gastric juice it is devoid of the irritating action of salicylates on the stomach, but it is decomposed by the alkaline intestinal juices setting free salicylic acid. In order, however, that its action may be entirely beneficial it is important to bear in mind that alkalis of any kind should not be administered immediately after aspirin. A weak acid, such as citric acid, is, on the other hand, a useful adjuvant.

The *salols* are also employed to avoid the ill effects of salicylic acid on the stomach. They pass through this organ unchanged, and are then decomposed by the alkalis of the intestine. In these circumstances *salol* itself (XXIX.) is then

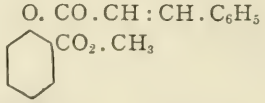
hydrolysed into salicylic acid and phenol. As the latter substance may in the long run produce toxic effects, an improvement on salol has been made by the Bayer Company, who have brought forward the product acetyl-para-aminosalol (XXX.), or *salophen*. This substance, like salol, is insoluble in the gastric juice, but when hydrolysed in the intestine it furnishes salicylic acid and acetyl-para-aminophenol, an innocuous product like para-aminophenol itself (*see* p. 572), which is eliminated without further change.

Mesotan (Bayer Company), $HO.C_6H_4.CO_2.CH_2.OCH_3$, another drug of this class, is chiefly employed in external applications for the local treatment of rheumatic and gouty affections; it is used as a substitute for oil of wintergreen, and is free from the disagreeable properties of this substance.

Although benzoic acid is a comparatively inert substance, the introduction of a double linking between the carboxyl group, CO_2H, and the benzene nucleus leads to the formation of a more physiologically active compound, namely cinnamic acid (XXXI.).



XXXI.

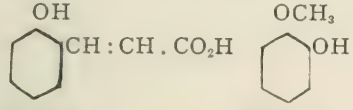


XXXII.

Drs. Jowett and Pyman, of the firm of Burroughs, Wellcome & Co., have endeavoured with success to combine the useful properties of salicylic and cinnamic acids in methyl cinnamylsalicylate (XXXII.), a compound which has been exhibited in rheumatism and allied conditions with excellent results, being tolerated in cases where aspirin has given rise to dyspeptic symptoms. When given with quinine it prevents the headache and other symptoms of quinism observed in those who are sensitive to this alkaloid. Cinnamic acid in the form of its sodium salt has been recommended in early cases of tuberculosis. When injected intravenously into animals it produces a marked increase in the number of white corpuscles, many of which assume a more active form, indicated by a more granular appearance of their protoplasm. This phenomenon is known as leucocytosis, and this increased activity of the leucocytes is an important factor in the combat incessantly waged by these cells, and more particularly their

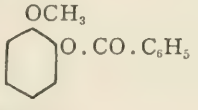
active polymorphonuclear forms, against the germs of disease. In Germany a dilute aqueous solution of sodium cinnamate is employed subcutaneously under the name of *hetol*. A solution of this salt in glycerine was suggested for the same purpose by the writer of this article in 1902. An 11 per cent. solution in this solvent is quite stable and free from any tendency to deposit crystals. The high temperature required for its production ensures its sterility, and its viscidity prevents a too rapid mixing of the solution with the blood stream, and thus promotes a more sustained local action. The physiological activity of cinnamic acid is undoubtedly due to its unsaturated ethylene linking, and in this connection it is interesting to notice that an even more unsaturated acid, namely, phenyl-propiolic acid, $C_6H_5 . C \vdots C . CO_2H$, which contains a treble (acetylene) linking, has been used for laryngeal and pulmonary tuberculosis in the form of its sodium salt under the designation of *thermiol*.

An extension of this cinnamate treatment to cases of malignant disease has led to the employment of substances combining the properties of salicylic and cinnamic acids, and the writer has suggested the use of the three isomeric coumaric acids. Of these isomerides the ortho-acid (XXXIII.)



XXXIII.

XXXIV.



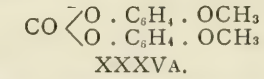
XXXV.

has given the most promising results, both clinically and in germicidal experiments *in vitro*.

The carbolic acid coefficients of germicidal value in respect of *Bacillus typhosus* estimated by the Rideal-Walker method are 6·5 for ortho-coumaric acid, 4·5 for the meta-acid, and 4·0 for the para-acid. These alkali coumarates and *tylmarine*, a preparation of the ortho-acid suitable for internal application, have been prepared by Messrs. Martindale.

Guaiacol, the monomethyl ether of ortho-dihydroxybenzene, a substance either obtained from beechwood tar or produced synthetically from ortho-anisidine, $CH_3O . C_6H_4 . NH_2$, is frequently indicated in tuberculosis, either free or in combination. *Benzosol*, prepared by Messrs. Meister, Lucius & Brüning, is guaiacol benzoate (XXXV.), which is split into guaiacol and

benzoic acid in the intestine. *Duotal* and *creosotal*, prepared by the Bayer Company, are respectively the guaiacol (XXXVA) and creosol carbonates,



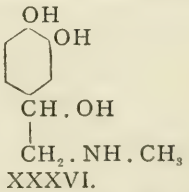
XXXVA.

which exert a favourable action on tuberculous conditions without irritating the stomach.

Synthetical Suprarenine

The synthetical medicaments described above have been employed as substitutes for the naturally occurring drugs, from which they generally differ entirely in chemical structure. The antipyretics of the phenacetin and antipyrin series have been used successfully as quinine substitutes, but nevertheless they do not resemble this alkaloid in chemical constitution. These differences are, moreover, not without their physiological counterpart, for in one respect at least the synthetical febrifuges differ from quinine, and that is in having no specific action in malaria, a malady in which the alkaloid exerts a well-defined beneficial influence. In this section an example of the successful synthesis of a naturally occurring drug will be discussed.

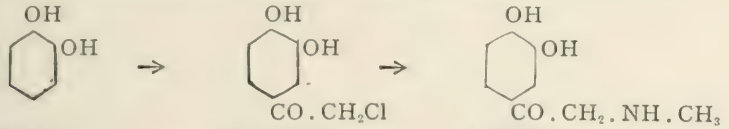
In 1901 Takamine and Aldrich, working independently, succeeded in isolating in a crystalline condition the active principle of the suprarenal capsules. This substance, which exerts an extremely potent influence in raising the blood-pressure, is the most powerful hæmostatic and astringent known. Its constitution was investigated by Von Fürth, Pauly, and Jowett; and in 1904 the last of these investigators indicated three formulæ for the base, stating that he considered that of these the following (XXXVI.) was the most probable:



XXXVI.

A compound having this constitution has since been synthesised by Messrs. Meister, Lucius & Brüning, which appears to have chemical and physiological properties identical with

those of the naturally occurring base. In carrying out this synthesis, catechol (XXXVII.) (ortho-dihydroxybenzene) is treated with chloroacetic acid, $CH_2Cl.CO_2H$,



XXXVII. XXXVIII. XXXIX.

the resulting chloroacetylcatechol (XXXVIII.) is then allowed to interact with methylamine, whereby methylaminoacetylcatechol (XXXIX.) is produced. This substance when reduced is converted into synthetical suprarenine, XXXVI. This base, which is sold in the form of an aqueous solution of its hydrochloride with sodium chloride, can be obtained much more cheaply than the naturally occurring substance. It is, moreover, stable in these circumstances, whereas the natural product undergoes decomposition fairly rapidly. It may be pointed out in passing that this very active drug has received at least three different names—viz. *adrenaline*, *epinephrine*, and *suprarenine*.

Iodoform Substitutes

Space does not admit of more than a brief reference to the synthetical products advocated as substituents for the powerful antiseptic, iodoform, CHI_3.

Isoform (Meister, Lucius & Brüning) is para-iodoxyanisole, $CH_3O.C_6H_4.IO_2$, a substance which is applied either as a dusting powder or in the form of paste; it is prepared from para-anisidine, $CH_3O.C_6H_4.NH_2$, by converting this base successively into its diazo-salt and then into para-iodoanisole, $CH_3O.C_6H_4I$. This product is treated with chlorine, the dichloride hydrolysed into the para-iodosoanisole, $CH_3O.C_6H_4.IO$, and then the last compound heated in steam, whereby equivalent proportions of para-iodoanisole and para-iodoxyanisole are obtained.

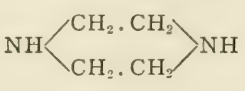
Aristol is an iodo-thymol, whereas *europhen* is isobutyl ortho-cresol iodide; both of these are recommended by the Bayer Company as iodoform substitutes.

Uric Acid Solvents

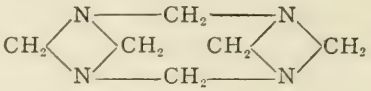
The treatment of gouty disorders with lithium salts has been almost superseded by the application of various synthetical

bases, many of comparatively simple structure, which exercise a marked solvent action on uric acid.

Piperazine, or diethylenediamine (XL.):

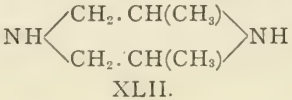


XL.

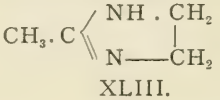


XLI.

is prepared by the interaction of ammonia and ethylene dibromide; it is administered both in the free state and also in the form of its salts, such as the phosphate or tartrate. The internal application of piperazine is followed by an increased elimination of urates from the system, and it is accordingly indicated in cases of chronic gout. Dimethylpiperazine, XLII.



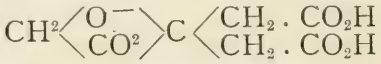
XLII.



XLIII.

(as the bitartrate, *lycetol*), has also been employed in this connection, and so also has *lysidine*, ethylene-ethenyldiamine (XLIII.), a base isomeric with piperazine, which in the form of its bitartrate is stated by Meister, Lucius & Brüning to dissolve eight times more uric acid than piperazine.

Hexamethylenetetramine (XLI.), the base produced by the interaction of formaldehyde and ammonia employed in the form of its salt with anhydromethylenecitric acid



and even the sodium salt of this methylenecitric acid alone, have been employed in this connection, the former under the name of *helmitol*, the latter being termed *citarin*. Hexamethylenetetramine itself has found employment as a diuretic and solvent of uric acid concretions under the name of *urotropine*.

Synthetical Drugs containing Metallic or Metalloidal Elements

There is a growing tendency to employ in therapeutics the organic derivatives of the metals and metalloids in preference to their inorganic compounds, as it not infrequently happens that in this way the element is more readily tolerated, and consequently can be administered with safety in larger doses.

For this reason mercury, copper, and silver salts of the organic acids are frequently employed both internally and externally. *Asterol*, a double salt composed of mercuric phenolsulphonate and ammonium tartrate, is stable in water, and neither precipitates albumin nor attacks metallic surgical instruments. Metallic salts of the organic acids are recommended as antiseptics. *Alumnol* is an aluminium β-naphthol-disulphonate put forward by Meister, Lucius & Brüning. *Nizin*, a zinc salt of sulphanilic acid $(NH_2 . C_6H_4 . SO_3)_2Zn.7H_2O$, is recommended by Messrs. Burroughs, Wellcome & Co. as a non-irritating, non-toxic antiseptic, which even in strong solutions does not coagulate albumin.

Copper cinnamate (*cuprocitral*) has been used in the form of an ointment in ophthalmic work. Strontium cinnamate has been tried in connection with the treatment of tuberculosis already mentioned.

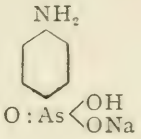
Bismuth salicylate and bismuth cerous salicylate have been employed in intestinal troubles, whilst bismuth subgallate finds employment as a non-irritant antiseptic dusting powder, under the name of *dermatol*.

Arsenic furnishes a good example of an element which is much more readily tolerated in the form of an organic salt. For this purpose sodium dimethylarsinate

$$(CH_3)_2 AsO . ONa, 3H_2O$$

was formerly advocated, as it is less poisonous than Fowler's solution (potassium arsenite). The use of this substance is, however, attended with one disadvantage—namely, the production in the system of malodorous cacodyl derivatives. A much more satisfactory vehicle for the therapeutic application of arsenic has been found in the substance known commercially as *atoxyl*, and which is prepared in a crystallised form by Messrs. Poulenc Frères and also by Messrs. Burroughs, Wellcome & Co. This compound was originally obtained by Béchamp in 1863 by heating aniline arsenate at 190–200° C., whereby a substance was formed which he considered was an anilide of arsenic acid, $C_6H_5 . NHAsO(OH)_2$. On neutralising this substance with sodium hydroxide a soluble crystallisable salt was obtained which was supposed by Béchamp, and more recently by Fourneau (1907), to have the constitution $C_6H_5 . NH . AsO(OH) . ONa$, together with some

water of crystallisation. The properties of the salt do not, however, correspond satisfactorily with this formula, and since the compound has come into use as a drug its constitution has been revised by Ehrlich & Bertheim. Their results, published in the *Berichte der deutschen chemischen Gesellschaft* for July 20th, 1907, show that in reality the substance is a salt of para-aminophenylarsinic acid having the following graphical formula—



and the commercial product generally contains four molecules of water of crystallisation. By analogy with sulphanilic acid, $NH_2 . C_6H_4 . SO_2 . OH$, the free acid has been called arsanilic acid, $NH_2 . C_6H_4 . AsO(OH)_2$, and accordingly atoxyl may be termed sodium arsanilate, $NH_2 . C_6H_4 . AsO(OH)ONa$, $4H_2O$. In this substance, the arsenic is very tenaciously held by the organic radicle, and is split off only under the influence of fused potash or by the action of hot hydriodic acid. The strength of the connection between the arsenic and phenyl is probably correlated in some way with the therapeutic action of the salt, for it has been found that atoxyl is forty times less poisonous than Fowler's solution. The salt may be applied either internally or externally; it has been indicated in several maladies, among others in tuberculosis and various skin troubles. Of special interest at the present time are the promising results which have attended the use of atoxyl in cases of sleeping sickness. Although it is as yet too soon to claim any specific action for the drug in this or other diseases, yet it is already evident that in this organic arsenic derivative we have a valuable therapeutic agent.

Although this review of the modern synthetical drugs is unavoidably brief and incomplete, it is hoped that it will serve to throw some light on the chemical nature of these substances many of which are at present in everyday use.

THE ELECTROLYTIC REDUCTION OF ORGANIC SUBSTANCES

By PERCY A. HOUSEMAN, Ph.D. (Würz.), A.I.C.

Organic substances capable of electrolytic reduction may be divided into two classes: (1) easily reducible substances, *i.e.* those which are reduced at any cathode; (2) difficultly reducible substances—those which are reduced only at cathodes possessing a particularly high "super-tension," limited practically to cathodes of lead and mercury. These two classes will be considered separately.

The method, briefly outlined, consists in allowing the hydrogen evolved from the cathode to act upon the organic substance, which is dissolved in a suitable solvent—usually sulphuric acid or aqueous or alcoholic alkali. The substance does not need to be an electrolyte, for the action is a purely chemical reduction by the hydrogen liberated at the cathode. Different chemical agents often lead a reduction in different directions, or arrest the same at different phases; and in the electrolytic process this finds a parallel in the regulation of the course of the reduction by variations in the cathode material—current strength, and, in the case of easily reducible substances, more particularly by the potential,[1] which regulates the pressure under which the ions are discharged from the solution, *i.e.* the energy with which the liberated hydrogen is capable of reacting. A higher potential corresponds in action to the use of a stronger chemical reducing agent.

In a similar way, choice of the size of the electrodes gives the power of regulating the concentration of the discharged ions, *i.e.* the number of ions liberated per unit of cathode surface, this factor also influencing the course of electrolytic reductions.

The earlier work was done on easily reducible substances by

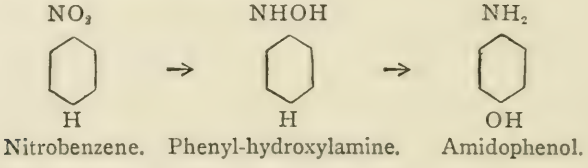
[1] Haber, *Zeitschr. f. Electroc.* 4 (1898), 506; *Zeitschr. f. phys. Chem.* 32 (1900), 193.

Gattermann, Elbs, Haber, Häussermann, Löb, and others. All these investigators paid special attention to the electro-reduction of the nitro- (NO_2) group in aromatic compounds—in particular nitrobenzene—both as a preparative method and also from a purely physical standpoint.

The first experiments on electro-reduction (as well as electro-oxidation) of organic substances were made between 1875 and 1886 by Goppelsroeder,[1] who worked on the production and bleaching of dyestuffs by means of electrolytically produced hydrogen and oxygen. From aniline sulphate by electro-oxidation Goppelsroeder obtained aniline-black, while potassium thiocyanate on electrolytic reduction yielded the dye canarin.

More important, both practically and theoretically, was the work of Gattermann on the electro-reduction of nitrobenzene and its derivatives. The chemical reduction of this substance yields, according to the reducing agent employed, azoxybenzene, azobenzene, hydrazobenzene, aniline, and benzidine. All of these products may also be obtained with the help of the electric current, variations in the conditions of electrolysis corresponding, as noted above, to the use of different chemical reducing agents.[2]

Gattermann,[3] however, and independently Clement and Noyes,[4] succeeded in obtaining an electro-reduction product of nitrobenzene, which all chemical agents had failed to yield, viz. para-amido-phenol. As an intermediate product phenyl-hydroxylamine is formed, subsequently undergoing transformation to amido-phenol, thus:



Nitrobenzene. Phenyl-hydroxylamine. Amidophenol.

Corresponding amidophenols were obtained under similar conditions from other aromatic nitro-compounds, such as nitro-toluene, dinitrobenzenes, etc. When nitrobenzene is reduced

[1] Oesterreich's *Wollen und Leinen Industrie*, Reichenberg, 1885.
[2] See scheme on p. 592.
[3] *Ber. der. deut. chem. Gesell.* 26 (1893), 1849.
[4] *Ibid.* 990.

in alcoholic alkaline solution, the chief products are the azo- and azoxy-compounds, while in acid solution the reduction is carried further, and the hydrazo- and amino-compounds are chiefly formed. This difference in the phase to which nitrobenzene is reduced in alkaline and acid solution, Löb ascribes, in the case of an alkaline solution, to the liberated sodium causing the reduction rather than the nascent hydrogen.[1]

Häussermann[2] was the first to obtain benzidine—

$$NH_2 - C_6H_4 - C_6H_4 - NH_2$$

as an electro-reduction product of nitrobenzene, Löb[3] subsequently obtaining benzidine in excellent yield by reducing first to the azo-phase in alkaline solution, and completing the reduction in dilute sulphuric acid solution. Löb also reduced many derivatives of nitrobenzene, such as the nitrobenzoic acids.

The first attempt to follow these electro-reduction processes quantitatively was made by Elbs,[4] who showed that the reducibility of nitro-compounds diminished as the number of nitro groups is increased. The quantitative investigation of these processes was, however, much more fully worked out by Tafel for difficultly reducible substances, and is described later.

Löb[5] called attention to the effect of different kinds of cathodes on the reduction of nitrobenzene, a factor which is of primary importance with difficultly reducible substances. Thus tin and copper electrodes yielded more aniline, nickel more azoxybenzene. Elbs[6] also showed that under otherwise equal conditions, nitrobenzene was more quickly reduced at a lead cathode yielding more aniline, than at a platinum cathode, at which more amidophenol was produced.

The following scheme shows at a glance the different reduction products which nitrobenzene has yielded, the reduction of this substance, and of its derivatives, by means of the electric

[1] Löb, *Zeitschr. f. Electroc.* 2 (1896), 529.

[2] *Chem.-Ztg.* 17 (129).

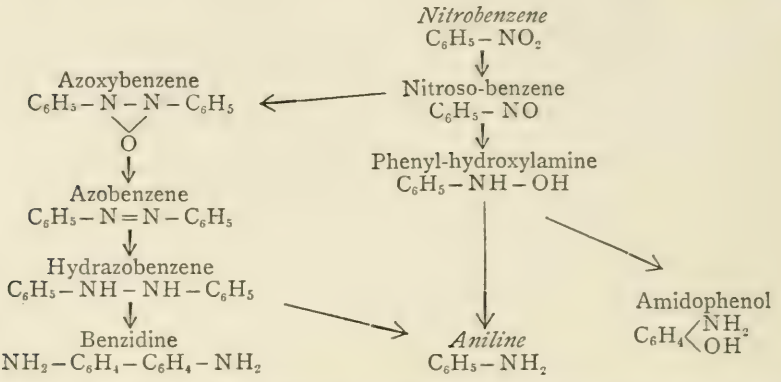
[3] *Zeitschr. f. phys. Chem.* 34 (1900), 641; *Zeitschr. f. Electroc.* 7 (1900), 320.

[4] *Journ. f. prak. Chem.* 43 (1891), 39.

[5] *Zeitschr. f. Electroc.* 4, 430; Löb and Moore, *Zeit. f. phys. Chem.* 47 (1904), 418.

[6] *Zeitschr. f. Electroc.* 2, 472.

current, having been of considerable theoretical and practical importance.



We turn now to the second class—the electrolytic reduction of *difficultly* reducible substances. This subject is a more recent one. The first such reduction was carried out by Tafel[1] on strychnine in 1898, to be followed in rapid succession by a large number of other compounds, so that the method has become one of great importance not only as a preparative method, but also in view of the many physico-chemical problems involved.

The advantages of the electro-reduction of organic substances —more particularly of difficultly reducible substances—will be considered briefly at the conclusion of the article.

A short description of the method and apparatus employed by Tafel for the quantitative investigation of these reductions must now be given.[2] Experiments must be made on a small scale to see firstly if the substance is capable of being electrolytically reduced at all, and secondly to determine the influence on the time required for the reduction of variations of current concentration,[3] current density,[4] etc. The time required is an important factor, as many of the products obtained are easily decomposable. Such preliminary experiments are made in the closed apparatus shown in fig. 1.

The lead beaker (A) serves as anode. The porous cell (B) separates anode chamber from cathode chamber. The cathode

[1] *Annalen*, 301 (1898), 285.

[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 2209; *Zeitschr. f. phys. Chem.* 34 (1900), 187.

[3] Current concentration = current per litre of cathode liquid.

[4] Current density = current per square centimetre of cathode surface.

chamber is closed by a well-fitting trebly bored rubber stopper, the centre hole of which carries the solid lead cathode (C), while the other holes are fitted with a thermometer (T) and a tube (D) for leading off the evolved hydrogen.

Connected in the same circuit is a second exactly similar apparatus, which contains sulphuric acid only, and *no* organic substance.

The evolved hydrogen from each cell is collected from time to time in a specially constructed pneumatic trough during a

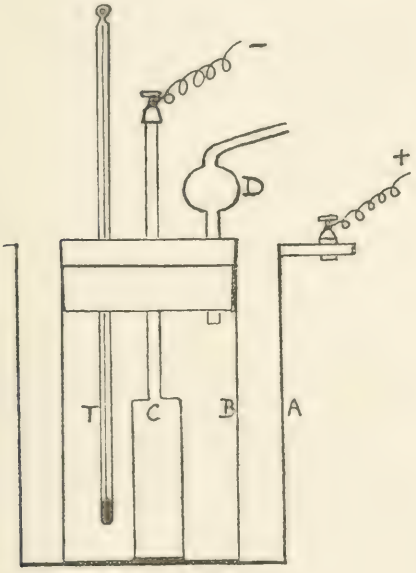


FIG. 1.

period of one minute. The difference in the two volumes (v-h) shows how much hydrogen has been used up by the process of reduction, and is a direct measure of the course of the reduction at that moment.

If this difference (v-h) is graphically plotted against time, a curve of the velocity of reaction is obtained. Fig. 2 shows a typical curve taken in this case for caffeine. It will be seen that the volume of hydrogen used diminishes regularly with the amount of unreduced substance remaining in the solution. One great advantage which such curves possess is that the area enclosed by the curve and the axes OA·OB is a measure of the total hydrogen used for the reduction. A comparison

between the total hydrogen used and that theoretically required by an equation gives valuable assistance in following the course of the reduction and in knowing what products may be expected. Thus, from the curve in fig. 2 the enclosed area when measured up represents a volume of 2,250 cc. while the equation

$$C_8H_{10}O_2N_4 + 4H = C_8H_{12}ON_4 + H_2O$$
Caffeine Desoxycaffeine

requires (for 10 grams of caffeine) 2,303 cc. hydrogen—the difference between the observed and calculated amounts being well within the limits of experimental error.

It has already been mentioned that the cathode material affects the reduction of aromatic nitro-compounds. With difficultly

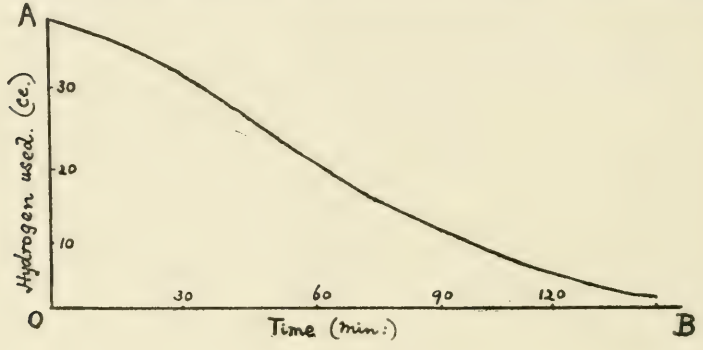


FIG. 2.

reducible substances, such as caffeine and uric acid, a reduction at any other cathode than mercury or lead is seldom possible.

The cause of this important fact is that the hydrogen from a lead cathode is evolved at a higher potential, and therefore possesses greater energy than the hydrogen evolved, say from a platinum cathode. This is intimately connected with the high "super-tension" of lead. Caspari[1] showed that the tension at various cathodes at which gaseous hydrogen visibly escapes differs widely. For lead and mercury this tension is highest—for platinum lowest. The excess of potential over that of a reversibly working hydrogen-oxygen-sulphuric acid element Caspari called the "super-tension" of the metal in question. The following are the values for the "super-tension" of a few metals:

Mercury 0·78 volt.	Lead 0·64.	Copper 0·23.
Silver 0·15.	Gold 0·02.	Platinum 0·005.

[1] Caspari, *Zeitschr. f. phys. Chem.* 30 (1899), 89.

It is this property of rendering difficult the escape of the hydrogen, which lead and mercury possess in such high degree, that allows the reduction of these difficultly reducible organic substances to be accomplished—while at all other cathodes they remain unaffected.

Quantitative experiments such as those already described show that the time required for the reduction is least by using a small current *density* (*i.e.* a large cathode) and as high a current *strength* as is compatible with holding the temperature within the necessary limits. When working on a larger scale, cooling (by means of hollow electrodes) is usually necessary.

One of the most interesting phenomena connected with this subject, and one which is also intimately correlated with "super-tension," is the poisonous influence of traces of foreign metals in the cathode chamber. Tafel[1] has shown that ·004 milligram of platinum per ten square centimetres of cathode surface is sufficient to bring the reduction to a standstill immediately. The other enemies of electro-reduction arranged in order are, after platinum, silver, tin, copper, mercury, zinc, and iron; though none approach platinum in its efficacy in causing the "spontaneous depression" of the reduction.

The most obvious explanation of this action is that the platinum is electrolytically precipitated on the surface of the cathode, and that then one is dealing virtually with a platinum cathode, which, as has been already shown, by reason of its low super-tension, *i.e.* the ease with which it allows the hydrogen to escape as gas, does not permit of the reduction being accomplished. Tafel's[2] extensive researches on this problem show that, not only is the amount of platinum present far too minute to form even the thinnest possible skin on the surface of the cathode, but also the action is different on different cathodes, and further, gold, which has almost as low a super-tension as platinum, should have quantitatively almost as great a disturbing effect, whereas gold is not nearly so poisonous to a lead cathode as platinum.

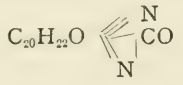
The conclusion is drawn that the platinum must exercise a catalytic influence on the surface of the cathode material. The disturbing action of minute traces of platinum and other metals has been one of the great difficulties in the application of

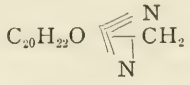
[1] *Zeitschr. f. phys. Chem.* 34 (1900), 187-228.

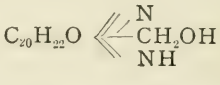
[2] Tafel and Emmert, *Ibid.* 52 (1905), 349.

Tafel's electro-reduction process as a preparative method, though the physical researches to which he was thereby forced have revealed much that is theoretically of considerable importance.

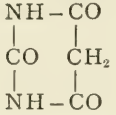
The electric current has been most prolific in the preparation of products which cannot be obtained by other reducing agents. A few of these may be mentioned as typical examples: Strychnine,[1] the first of these substances to be submitted to electrolytic reduction, yielded strychnidine and tetrahydro-strychnine, both these substances possessing in a less degree the same physiological action as strychnine.

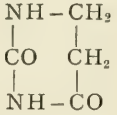

Strychnine.

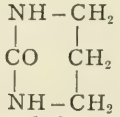

Strychnidine.


Tetra-hydro-strychnine

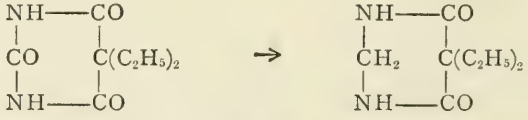
As an example from the ureides, barbituric acid[2] may be cited, this substance yielding on reduction a mixture of hydro-uracil and trimethylene-urea.


Barbituric acid


Hydro-uracil


Trimethylene urea

The behaviour of di-ethyl-barbituric acid,[3] which is now being used somewhat extensively as a soporific under the name of Veronal, is very remarkable. Instead of being reduced in a manner analogous to barbituric acid, the hydrogen attacks the urea residue thus:—

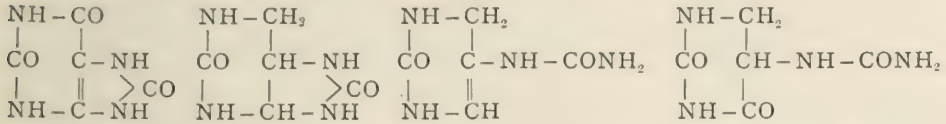


Up to the present this is the only observed instance in which the carbonyl (CO) group of the urea chain has been electrolytically reduced.

Of particular interest are the electro-reduction products of uric acid,[4] inasmuch as this physiologically important body has not been directly reduced by any other means, if one leaves out of account the breaking down of the molecule by hydriodic

[1] *Annalen*, 301 (1898), 285.
[2] *Ber. d. deut. chem. Gesell.* 33 (1900), 3383.
[3] Tafel and Thompson, *Ber. d. deut. chem. Gesell.* 40 (1907), in press.
[4] *Ibid.* 34 (1901), 258.

acid. Three substances are obtained by the electrolytic reduction of uric acid—puron, isopuron, and tetra-hydro-uric acid. The manner in which the hydrogen is added on is seen clearly from the following formulæ.



Uric acid Puron Isopuron [1] Tetra-hydro-uric acid

It will be noticed that puron and isopuron are isomeric, *i.e.* they possess the same empirical formula, $C_5H_8O_2N_4$. The former is transformed to the latter by treatment with caustic alkali.

The methyl derivatives of uric acid [2] also yield a series of corresponding methyl derivatives of puron and isopuron. In no case, however, is a substance corresponding to tetra-hydro-uric acid produced.

The slightly higher super-tension of mercury than lead is the cause of some substances being reduced better with a cathode of the former metal than with one of the latter.[3] Examples are acetone and caffeine. In the case of camphor no reduction whatever takes place at a lead cathode, while, with a mercury cathode, borneol is obtained in good yield.

It is to be expected that the electric current will come more and more into use as a preparative method for the reduction of organic substances. By varying the potential one can, as Nernst expresses it, produce pressures whose amount varies between very small fractions of an atmosphere, and many million atmospheres; and this is the reason why the electric current accomplishes the reduction of some substances, such as uric acid, which remain entirely unaffected by the ordinary chemical reducing agents.

The successful clearing away of the many preliminary difficulties leaves the method a well-understood and comparatively simple one, besides which, electro-reduction possesses the further advantage of the absence of other reagents, which usually entail a more or less troublesome process of elimination in the course of reduction by the usual chemical agents.

[1] Tafel and Houseman, *Ber. d. deut. chem. Gesell.* 40 (1907), 3743 (in press). Houseman, *Dissertation*, Würzburg, 1906.

[2] *Ber. d. deut. chem. Gesell.* 34 (1901), 279.

[3] Tafel and Schmitz, *Zeitschr. f. Electroc.* 8 (1902), 280.

DIFFUSION AND ENTROPY OF GASES

By S. H. BURBURY, F.R.S.

1. This subject has been treated by Lord Rayleigh in *Phil. Mag.* January—June 1875, under the title "On the Work that may be gained by the Mixture of Gases," pp. 311, 318, and by Prof. Bryan in his recent work on *Thermodynamics* (Leipzig: Teubner). Each writer's work presents some difficulties, which I propose to consider in the present paper. Rayleigh's argument is based on the fact that hydrogen escapes through fine apertures more rapidly than air, even at greater pressure, enters to supply its place. His conclusion is that "the work that may be done in the mixing of volumes v_1 and v_2 of two different gases is the same as would be gained in the expansion into vacuum of the first gas from volume v_1 to $v_1 + v_2$, together with that which would be gained by the expansion into vacuum of the second gas from volume v_2 to $v_1 + v_2$." It is understood that the gases follow the law of independent pressures, each behaving as a vacuum to the other. The law is thus stated with complete generality, and without qualification as to the nature of the containing materials or otherwise. Bryan states the law in substantially the same form at p. 125 of his work. I therefore call it the Rayleigh-Bryan law.

2. The thing to be proved, as I understand it, is this: that two physically different gases, if separated, can be made to do mechanical work, at the expense, of course, of their heat, in mixing; on the other hand, if they mix by diffusion, no work is done. Therefore by allowing them to mix by diffusion, we lose the opportunity of converting heat into work, *i.e.* we lose the "available energy" which they had by virtue of their separation.

3. Before discussing the arguments in detail, it will be well to calculate the work that can be done in case of two gases, one of which is hydrogen, in a cylinder of volume $2v$, separated, as Rayleigh suggests, by a piston porous to the hydrogen, but hypothetically impermeable to the other gas, say oxygen. They

are supposed to be both at the same pressure, p, and the same temperature, and each initially occupying volume v. Also the temperature is maintained constant notwithstanding the conversion of heat into work during expansion of either gas. The piston being fixed, hydrogen escapes through it, until it is of the same density throughout the cylinder, oxygen behaving as a vacuum to it. This being done, the pressure is $\frac{3p}{2}$ on the oxygen side, and $\frac{p}{2}$ on the hydrogen side. The piston being now set free, the oxygen expands, and if its expansion takes place very slowly, the hydrogen, as it can pass through, will be throughout the process at the same pressure on either side of the piston. The work done by expansion of the oxygen is then the same as if the hydrogen were absent, and is

$$\int_0^v \frac{pv}{v+x}\,dx = pv \log 2.$$

It is therefore exactly half the work required by the Rayleigh-Bryan law. At the end of the process the two gases are uniformly mixed throughout the volume 2v of the cylinder. No further work can be obtained from the system while it is in that state. If the piston, instead of being impermeable to oxygen, were permeable by it, only in less degree than by hydrogen, the work obtained would be less—that is, less than half the work required by the law.

4. We must now consider Rayleigh's arguments. They seem designed to show that the separation of mixed gases generally involves the expenditure of work, and that this work may be regained in their mixture. In his first example a mixture of steam and hydrogen under a piston in a cylinder of volume v is compressed, the temperature being maintained constant, until at volume v_1, the saturation point of the steam is reached, and it begins to liquefy, and is all liquefied at volume v_0. I understand Rayleigh to say that at this point all the hydrogen exists as gas between the water and the piston, none being held in solution by the water. The water is then put in a separate vessel, and is evaporated and expanded to its original volume and temperature. The hydrogen also expands to its original volume and temperature. The work gained in expansion is, he says, equal to that spent in compres-

sion, so that in the complete cycle, the whole system being restored to its original state but for the separation of the gases, no work on the whole is done. Does this result support Rayleigh's doctrine? It is true work is spent during the separation, and gained during the subsequent expansion—that is, the gases when separated have available energy. But this is not because they are separated, but because they are compressed, and they would have precisely the same available energy if they were not separated at all, but expanded as a mixture to their original state.

5. In his second example Rayleigh shows how the separation of two gases may in a certain case, and doubtless in other cases, be effected by chemical means.

6. In the third argument (p. 313, etc.), Rayleigh considers the case in which two gases, a heavier and a lighter, say oxygen and hydrogen, are partially separated by the action of gravity in a vertical tube. Suppose them to have arrived at a state of equilibrium, and the partial pressures at the base of the tube are the same as those of the same two gases mixed in a reservoir, so that if the tube communicates with the reservoir at its base no oxygen or hydrogen escapes from or to the reservoir. Rayleigh proves that if the mixture of gases in each element of the tube be separately compressed to the total pressure at the base, and is then brought down to the level of the base, the work spent in the compression exceeds in the case of two gases that gained from gravity in the descent. Were only one gas present, it would be equal to the work gained.

7. In order to make the cycle complete, except that at the end the gases are partially separated, at the beginning uniformly mixed, I will work out the problem independently. As will be seen, I shall obtain Rayleigh's result above stated. I consider two cases:

Case I.—A single gas is at uniform pressure and temperature in a horizontal tube ACB of length S. C is the middle point, and initially the centre of gravity of the gases. I avail myself of the permission given by Rayleigh (p. 318, line 3) to divide the tube into elements of length, and to insert between each pair of successive elements a piston, fixed or movable, to prevent passage of molecules from one element to another, also permission to remove such pistons. Then—

Process (1). Fix the pistons and turn the tube about the end

A into the vertical position. In that we spend work MgAC, if M be the mass of the gas. We need not take into account the mass of the tube.

Process (2). Set the pistons free, then compression ensues towards the base. The centre of gravity falls to C_1. We gain work from gravity MgC_1C, which is all spent in the compression.

Process (3). Again fix the pistons, and turn the tube about A into the horizontal position. In that we gain work $MgAC_1$.

Process (4). Let the gas expand till it reaches its initial uniform density. In that we gain work by the expansion equal to the work spent in compression, that is MgC_1C.

In all we have spent work MgAC in (1) and gained work $MgAC_1$ in (3) and MgC_1C in (4)—that is, we have spent zero work.

8. *Case II.*—Instead of a single gas, let there be in the horizontal tube equal numbers of molecules of oxygen and hydrogen uniformly mixed, then insert and fix the pistons, and perform Process (1) as before. In that we spend work MgAC as before, M being the combined mass of the gases.

Process (2). Set the pistons free, and compression takes place as before. The c g falls to C′, and the work of compression, which is done by gravity, is MgCC′.

Before Process (3) we must now interpolate a new process (2A)—namely, remove the pistons, so that diffusion takes place. The gases assume a new position of equilibrium, in which each behaves as a vacuum to the other.

If R_1 denote the density per unit of volume for oxygen at the base, r_1 its density at height s, and if R_2, r_2 be the corresponding densities of hydrogen, $r_1 = R_1 e^{-2hm_1gs}$, and $r_2 = R_2 e^{-2hm_2gs}$, m_1 being the mass of a molecule of oxygen, m_2 that of hydrogen —that is, oxygen partially replaces hydrogen in the lower, hydrogen replaces oxygen in the upper strata. The centre of gravity falls to C″. Before considering what becomes of the work thus gained MgC′C″, let us perform Processes (3) and (4). Fix the pistons, Process (3), and turn the tube about A into the horizontal position. In that we gain work MgAC″.

Up to this point we have spent work MgAC, and gained MgAC″.

Then Process (4), set free the pistons, and let the gases expand without diffusion till they attain uniform pressure, but not uniform mixture, throughout the tube. The work gained in

that expansion is equal to the work spent by gravity in the compression. If, then, the work gained from gravity in Process 2A, namely MgC″C′, is all spent in compression, there is in the complete cycle zero work spent.

But if, as I think is the case, part only of the work MgC″C′ is spent in compression, and part converted into heat, *i.e.* dissipated (see Raleigh's remarks, pp. 317-8), we have in the whole spent work equivalent to the dissipated energy.

9. Is not the theory this? If we had suitable machinery to act on individual molecules, *e.g.* if we could employ Maxwell's demons for the purpose, we might effect the separation of the oxygen and hydrogen molecules mixed in the horizontal tube without doing any work, no work being *essential* to the process, unless molecules of the same gas appreciably attract or repel each other, which is understood not to be the case. As we have no such machinery, and cannot employ the demons, we have to effect the separation by indirect processes, as in the example given. And these indirect processes generally involve dissipation. Work is spent in the separation of the gases, but the energy is in no sense available. Energy dissipated is unavailable.

Professor Bryan's Argument

10. I come now to Prof. Bryan's argument, which is mainly theoretical. I will give his proof of the law (for there is a logical proof) as I understand it. I begin with his definition of " entropy," the second of p. 58.

(*a*) If the unavailable energy of any system receives any positive or negative increase δQ, the entropy is increased by $\frac{\delta Q}{T_0}$, T_0 being the lowest available temperature. I think we may say, at least by way of example, without affecting the generality of this definition, that δQ is the heat which passes into the refrigerator in the lower isothermal of a Carnot cycle in which the system is the working substance.

(*b*) This being the definition of entropy, it follows that if the entropy increases, the unavailable energy increases. Therefore, since energy is either available or unavailable, if while the entropy increases no energy enters or leaves the system from or to external bodies, the available energy diminishes.

(*c*) The entropy of a system is a function of the physical

state of the system, and cannot change while that state remains unchanged. Therefore, if the system be a gas, at all events if a perfect gas, it may be expressed as a function of the temperature and volume—and, it may be, also a function of the number, n, of molecules in the given volume, say generally it is f(n, T, v).

(*d*) But, if the gas be the working substance in a Carnot cycle, the heat drawn from the reservoir in an isothermal expansion from volume v to volume v + δv is proportional to the pressure, that is, for given v, proportional to n. Therefore, also, the heat δQ, which passes into the refrigerator in the same cycle, is proportional to n. Therefore, if S_n be the entropy of a single gas containing n molecules in volume v, $S_{n'}$ the entropy for the same gas containing n′ molecules in volume v, $\frac{\delta S_n}{\delta S_{n'}} = \frac{n}{n'}$. And since S_n and $S_{n'}$ cannot differ by a constant, $\frac{S_n}{S_{n'}} = \frac{n}{n'}$. That is, $\frac{f(n, T, v)}{f(n', T, v)} = \frac{n}{n'}$ for all values of n and n′. This requires that f (n, T, v) = nφ (T, v), where φ (T, v) denotes some function of T and v. Therefore f (n + n′, T, v) = (n + n′) φ (T, v) = nφ (T, v) + n′φ (T, v), or the entropy of a single gas, in volume v, is the sum of the entropies of all the parts into which it may be conceived as divided, provided that each part is free to move throughout the whole of v, and is not confined by partition to a part of v. (N.B.—This is my own argument, and not Bryan's. It would not necessarily apply to two different gases, because the physical state of each might be affected by the presence of the other.) Bryan, however, proves the same thing for two gases as follows:

(*e*) The entropy of a gas occupying volume v is the same whether it has that volume all to itself, or shares it with another gas at the same temperature and pressure. In other words each gas is in respect of its entropy a vacuum to the other. *Query*, is there any limit to this law as the density increases?

A proof of this is given at p. 124 by the following method, which I understand to be founded on experiment. Given a mixture of two gases in cylinder of volume 2v, each having the same partial pressure ½p, and the mixture having combined pressure p, the mixture is cooled until the gases liquefy, one before the other. The liquids are put in separate vessels,

and evaporated, and heated until each occupies volume 2v, and is at the original temperature of the mixture. It is assumed (1) that the volumes of the liquids are negligible in comparison with their vapours; (2) that the specific heats are constant; (3) that the latent heat of evaporation of either component is unaffected by the presence or absence of the other. On these assumptions Bryan concludes that the process is reversible. Therefore entropy is the same at the end, when each gas has a volume 2v to itself, as at the beginning, when they had one volume 2v in common, *cæteris paribus*.

(*f*) The entropy of a gas in volume v increases, *cæteris paribus*, when v increases. This follows from the definition (*a*). For S denoting entropy, $\delta S = \frac{\delta Q}{T_0}$; therefore $\frac{dS}{dv} = \frac{1}{T_0}\frac{dQ}{dv}$, and $\frac{dQ}{dv}$ is always positive by the Carnot cycle.

11. We may now compare two states of a system: state A, two gases occupying each a volume v, separated by a partition, and each at pressure p, and temperature T; state B, the same two gases mixed in volume 2v, *cæteris paribus*. Each gas has in state A entropy $n\phi$ (T, v), and by (*e*) it has in state B entropy $n\phi$ (T, 2v), which by (*f*) is greater than $n\phi$ (T,v)—that is, each has greater entropy, and therefore the system has greater entropy in B than in A. Therefore the system has less available energy in B than in A, or available energy is lost in the process of mixing, no energy passing in that process from or to external bodies.

12. Evidently the amount of available energy that each gas loses in the process of mixing is measured by the entropy that it gains—that is, the difference of entropy between the gas occupying volume v, and the same gas *cæteris paribus* occupying volume 2v—that is, the available energy lost by the process is for each gas the available energy it would lose by expanding into vacuum from volume v to volume 2v, the temperature being constant. The Rayleigh-Bryan law is thus formally and completely proved in the sense of Bryan's definition of available energy, whatever that may be.

13. I note that Bryan's process of separating the gases (p. 124) involves no expenditure of work. If, therefore, the gases when separated have more available energy than when mixed, it is not because work has been spent in their separation which can be regained in their mixture, in which Bryan seems to differ from Rayleigh.

14. The argument (Bryan's) seems to prove too much, if I am right in (*d*) above. For if so, the argument applies equally to two portions of any single gas. Therefore, we could increase the available energy of a single gas by dividing it into two parts by a partition. Even if (*d*) be not accepted, does not the same thing follow from Bryan's proof (*e*) applied to two portions of the same gas? It is true that this process, although it separates two gases having different temperatures of liquefaction, cannot separate two portions of the same gas. But we may separate the two portions, and put them in separate vessels, immediately after or before liquefaction, and then evaporate them separately, till each attains its original temperature and original volume 2v. If the process is reversible for two gases, is it not equally reversible for two portions of the same gas? If so, then two portions of the same gas, each at the same temperature and pressure, mixed in one volume 2v, have more entropy than they would have if they each occupied volume v, and were separated by a partition.

15. Subject to the doubt raised in 14, the argument of arts. 10 and 11 seems logically conclusive, that two separated gases lose available energy, whatever that may mean, when allowed to mix by diffusion, and that the amount of available energy lost is that stated in the Rayleigh-Bryan law.

16. Nevertheless, it does not necessarily follow that the available energy lost is *the practical possibility* of transforming heat into work. For the only definition of available energy which we have used in the argument is that it diminishes with increase of entropy. In fact, if the entropy is a function of T and v, and independent of any conditions, the available energy must be a function of T and v, and independent of any conditions. It does not, therefore, follow that because a system loses available energy in passing from state A to state B, therefore we can actually transform heat into work given the system in state A. It may be that in state A work is *theoretically*, but owing to the external conditions not *practically*, derivable from the system. In Bryan's definition of available energy (p. 43) "work theoretically derivable" must mean "work which under suitable external conditions might be derived." If two separated gases (state A) are each at pressure p, and are surrounded by infinite air at pressure p and at the same temperature as the gases, no part of the heat of either gas can

be transformed into work while the whole system is what it is. We then call upon the experimental philosopher to convert it into something that at present it is not, but without initially altering its entropy. This he can do by substituting for the partition separating the gases a piston porous to one, but not, or not in the same degree, porous to the other. We might say paradoxically that, while the separated gases are separated, the available energy is not available; but when by using the porous piston the separated gases are not separated, the available energy, or some part of it, is available. A dinner is placed before Tantalus, and it is mathematically proved to him that it is an available dinner, but he is unable to eat or drink.

17. There may be other transformations of the system which would admit of work being obtained. One other method has been suggested—namely, a liquid which absorbs one of the two gases, but not the other. By such a liquid we might perhaps reduce one of the two gases to lower pressure than the other, and so render the performance of work possible. But that method might be applied with equal success to two separated portions of a single gas.

18. Bryan uses instead of the porous piston a membrane (p. 125). And he suggests the ideal case of two membranes, one of which is porous to gas (1), but wholly impermeable to gas (2), the other membrane *vice versa*. But should not this ideal combination of gases and membranes be required to prove its own existence before it is used to prove anything else? If Bryan says it does exist, I accept his authority.

19. Another line of argument to prove the Rayleigh-Bryan law, not expressly relied upon by Bryan, is as follows: If any irreversible process takes place in the interior of a system, the unavailable energy of the system, and therefore the entropy, is increased. And the mixture by diffusion of two gases originally separated is stated by Bryan to be an irreversible process. I admit the argument, if the diffusion is an irreversible process. But there is no proof that it is not a periodic process.

20. It is, of course, a familiar experience that two separated gases, each at the same pressure and temperature, if the partition be removed, at once begin to mix—or, let us say, if they are originally mixed in different proportions on the two sides of the partition, at once begin to assume a more uniform mixture. But

that phenomenon is as consistent with the motion being periodic as with its being asymptotic—*i.e.* irreversible. For if periodic, any point in the path may be described in either of two directions, typically the paths may be ABCA, or ACBA. By the way in which we make the experiment, we determine the direction to be that in which the initial motion is towards more uniform mixture, say ABCA, if B denotes the initial, and C a state of more uniform mixture than B. That is because initially the two gases are *at rest* relatively to one another. As an example, suppose a semicircular smooth tube in a vertical plane with its middle point as base, and in it a heavy particle. The particle, if free to move, and placed at rest at a point above the lowest, will begin by moving downwards. But it will oscillate about the lowest point, and will not move irreversibly to the lowest point. The reason why it begins by moving downwards is because it starts *from rest*. For precisely the same reason the two gases, each *at rest relatively to the other*, begin by moving towards the more uniform mixture. But there is no proof that the motion is irreversible.

21. It is true no man has ever observed them to begin to separate. But to make this evidence of the irreversibility, it would be necessary to continue the experiment for a time at least equal to half the period, if the motion be periodic. And not only that, but also to completely protect the system from all disturbances from without during the whole time. Has this ever been done? And as regards external disturbances, can it be done? If practically it cannot be done, then it may be that in any experiment that can practically be performed, the motion will appear to be irreversible, because the external influences prevent it from being periodic. But then they also prevent the argument from being applicable.

22. If the diameters of the molecules were so small that no collisions occurred, the motion must be periodic. Can it be proved that collisions convert it into an irreversible motion?

23. I think we unconsciously derive the idea of the motion being irreversible from Boltzmann's H Theorem, which is supposed to prove that an irreversible motion of a gas is possible, and that, I think—although the weight of authority against me is immense—rests on "a misuse of the theory of probabilities."

We suppose that at an initial instant the co-ordinates and

velocities of the molecules are distributed at haphazard, subject to the conditions (1) that the total kinetic energy is a given constant T, and (2) that Boltzmann's function H has a value greater than its minimum. And we then prove that $\frac{dH}{dt}$ is, under those circumstances, much more likely to be negative than positive. That is true. But the initial values of the variables having been once assumed, their values after any time t are determinate functions of the initial values and of t. The law of probabilities has nothing further to say in the matter, but having fixed the initial values is *functus officio.*

24. The error consists, as I maintain, after the manner that men call heresy, in assuming the law of probabilities to have continuous action, as though an independent haphazard distribution of the variables took place at every instant. If that were the case, it is true that $\frac{dH}{dt}$ would be on an average negative at every instant, and the motion could not be periodic. There are, in fact, at the initial instant a great number, say n, of possible states of the system, and as many possible determinate courses for all subsequent time. By the way in which we make the initial distribution, each of these n states, with its determined course, is as likely to happen as any other. Further, as we are in complete ignorance of the sequence of events in any one of the n courses, it is true that, to our minds subjectively, each state of the system is at every instant as probable as any other. But this ignorance of ours would exist in fact whether the motion be periodic or irreversible. We cannot therefore argue from our ignorance of the courses that the motion is irreversible. For this reason I think the usually accepted proof is illogical.

25. Further, the objection to the H Theorem, first made, I believe, by Loschmidt, that if all the velocities were at any instant reversed, the system would retrace its course, is, to my mind, fatal to any theorem of irreversible motion in a gas whose molecules are such as the kinetic theory assumes, provided that the isolation of the system be complete. Of course, if a fresh haphazard distribution took place at every instant, as the theory requires, the Loschmidt objection would fail altogether, for on reversal of the velocities the system would *not* retrace its course. And any external disturbance,

coming at haphazard, independently of the existing state of the system, effects a new distribution *pro tanto.*

26. I know it is said in defence of the theorem that the reversed motion, though possible, is highly improbable. But if the H theorem be true, Maxwell's law of distribution of the velocities must be assumed to prevail ultimately, or anyway cannot be denied by advocates of the theorem. From which it follows that any course and the reversed course are equally probable. To say that one of the two is the more probable *because it leads to H diminishing* would be a *petitio principii.*

27. If, as I think is the case, the complete protection of two diffusing gases from all external influences continuously for a very long time is impossible, the motion is, as I have said, for that reason irreversible, because the external disturbances are equivalent to a new haphazard distribution. But for that same reason the irreversibility does not necessarily involve increase of entropy, and the whole argument falls to the ground.

28. I have asserted generally that if the molecules of gases are what they are assumed to be in the kinetic theory, no irreversible motion is possible in an isolated system. Very probably it may be necessary to revise our conceptions of a molecule, and Prof. Bryan's work may well be conducive to that end.

THE PRICE OF ANÆSTHESIA

By AUGUSTUS D. WALLER, M.D., F.R.S., LL.D.

The debate that took place a few weeks ago through the columns of *The Times*, between the scientist who finds his public too ignorant to understand him and the public who finds that the scientist talks a learned jargon that is a sign and symptom of his own imperfect knowledge, is one that should not fail to be heeded by any person making bold to say something in the pages of Science Progress. For we are, all of us, in relation to each other's work and thought, very public indeed; the barrier of language is raised not only between scientists and public, but between scientists and scientists, and the public is hardly to be condemned as ignorant if the instructors themselves remain immured from each other, as well as from "the public," in their private apartments of thought and language.

If it be true that nothing new in science is achieved otherwise than by "constantly thinking unto it," it is equally true that "the greatest thing a human soul does in this world is to see something, and *tell* what it saw in a plain way.

I am perhaps rashly challenging an adverse verdict by proclaiming at the outset a standard of excellence that I may hardly hope to reach—that I shall, however, attempt to reach—by telling in a plain way something that I have seen.

Chloroform, the anæsthetic *par excellence*, that has conferred upon mankind the great boon of surgical anæsthesia, is known, or will one day be known, to the vast majority of us by actual personal experience. That is a first reason to enlist our interest. It is one of the most efficient and certain poisons known; its certainty and regularity of action are such that it is systematically used for mercifully getting rid of lost dogs, and an unknown but considerable number of persons annually lose their lives in consequence of chloroform administered for the purpose of producing surgical anæsthesia—"skilfully administered for a necessary surgical operation," to quote words frequently employed by coroners' juries. The number of officially

recorded deaths in England registered as due to anæsthetics during the ten-year periods was:

1866 to 1875	. . . . .	146 deaths.
1876 „ 1885	. . . . .	264 „
1886 „ 1895	. . . . .	533 „
1896 „ 1905	. . . . .	1,269 „

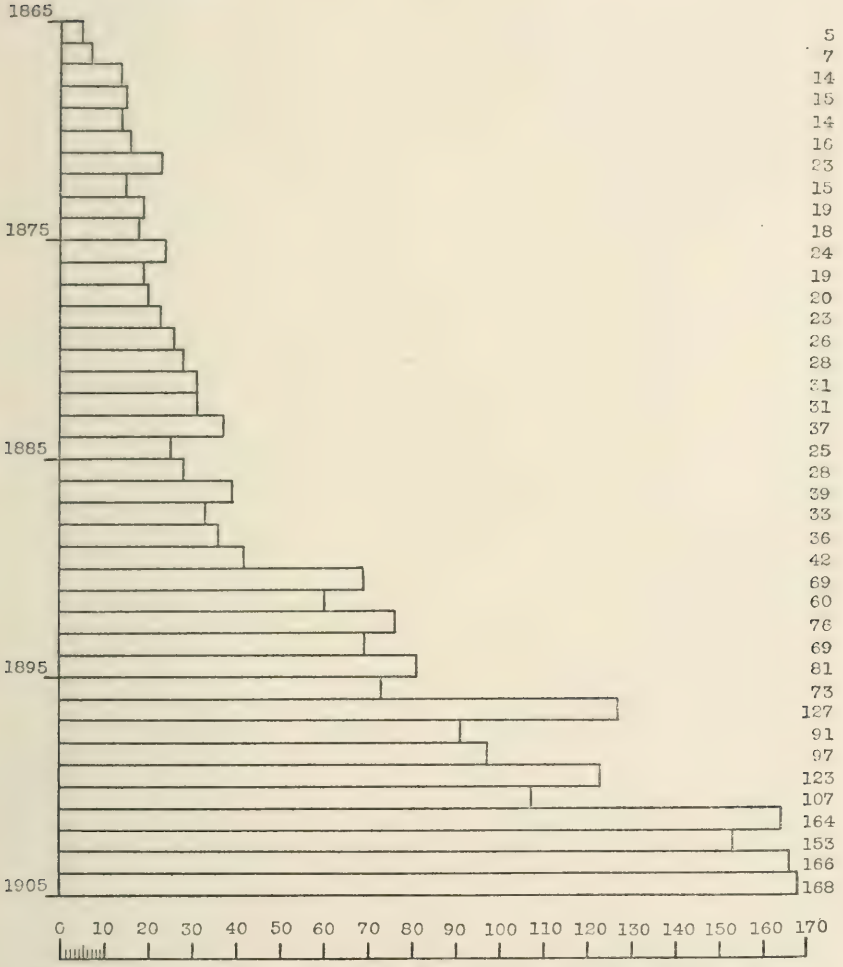


FIG. 1.—Diagram of the annual number of deaths registered in England and Wales as due to anæsthetics in the years 1865—1905.

Now, this is a heavy price to pay for even the great boon of anæsthesia; for it is an unnecessary price—a toll levied in

all good faith by reason of a neglect of the most elementary knowledge of the physical and physiological properties of chloroform.[1]

I do not say that such neglect is universal, and that there are not exceptional administrators of experience and natural skill such as to entitle them to be considered "safe," but I do say that the general practice of the overwhelming majority of persons, whether medical or non-medical, who are necessarily called upon to administer chloroform, is dangerous, and must unavoidably kill a certain number of patients and endanger the lives of many more, and produce an incalculable amount of alarm and uncertainty in connection with anæsthesia.

And I shall hope to show in the course of this article, so as to be understood by any educated person, medical or non-medical, that this heavy price is paid for lack of a little

[1] I do not think it necessary to enter here into any detailed discussion of the value of these statistics. It has been urged in mitigation of the figures that (1) they include many cases in which death has occurred not *by*, but only *after*, chloroform; and that (2) we should take into account the greatly increased number of operations performed under anæsthesia.

I think that the first error is far outweighed by the opposite error of attributing to other causes deaths that have in reality been due to the anæsthetic. A large proportion of cases of deaths undoubtedly due to chloroform are never published, or are attributed to other causes. How many it is impossible to say. Some years ago, when I went closely into the matter, I found in the case of one hospital, at which two cases had been reported in the year, that nine cases had actually occurred. The late Prof. Julliard, of Geneva, found that twenty cases of death by chloroform had occurred at Geneva, of which three only were reported. And only last January a London coroner, in opening an inquest, stated that "this is the thirty-ninth case of the kind from —— Hospital in the course of six and a half years."

In *The British Medical Journal* of January 25 (p. 202), a case of death during anæsthesia is reported by an anæsthetist under the title "A Fatal Case of Status Lymphaticus"; and the previous pages of the same issue contain an elaborate argument by another anæsthetist to the effect that death during chloroform anæsthesia is so frequently associated with "status lymphaticus" that it may be asked whether death under chloroform ever occurs apart from that condition.

Clearly the price of anæsthesia, as indicated in the returns of the Registrar-General, must be below rather than above the mark. With regard to the probable increased number of operations under anæsthetics during the last half-century, no doubt it has had some influence on the increased number of deaths noted for the later than for the earlier years, but it can hardly account for the figures of the last two decades, in which, while the reported deaths have more than doubled—533 and 1,269—the number of operations can hardly have increased in the same proportion.

elementary science—not science expressed in Græco-Latin neologisms, but science of the A B C character, consisting of simple arithmetical measurements, far less complex and learned-sounding than much of the science that is dispensed by board-school teachers and extension lecturers, but for lack of which even a doctor of medicine is not qualified to administer chloroform.

Let me premise in the first place that it is totally futile in the case of any poison, whether it be called strychnine or alcohol or aconite or morphia or chloroform, to discuss sources of danger, antidotes, diathesis, idiosyncrasy, etc., etc., without knowing how much strychnine or alcohol or chloroform has been put into the body. It is comparatively easy to learn how much strychnine will kill, rather less easy to know how much alcohol will intoxicate, comparatively difficult to determine how much chloroform will anæsthetise.

Alcohol is more or less measured out, by glass or bottle, and we know that the subject gets more or less drunk after more or less drink; knowing this we are justified in observing that subjects differ, and that qualities of liquor vary; and if necessary we can go on to consider effects of adulterations and effects of idiosyncrasy. But obviously we could do nothing of the sort unless we could measure quantities of poison swallowed.

But in the case of chloroform, which is administered by inhalation through the lungs, the effects of adulteration and the effects of idiosyncrasy have been discussed in the absence of any approach to such a measurement. The patient has as a rule inhaled an unknown quantity of chloroform. As a rule the administrator has not the slightest idea what the quantity has been, and a fatal accident that has in all probability been caused by overdose is put down to idiosyncrasy of patient or impurity of chloroform.

Is it not clear that the first necessary step to take, previous to any possible rational discussion of idiosyncrasies and impurities, is to find means of measuring the quantity of chloroform absorbed, or at any rate of measuring the quantity of chloroform in the air inspired?

My attention was forcibly directed to this question in 1890, in connection with physiological experiments. Whereas in my previous clinical experience I had had occasion to administer

chloroform fairly often in the rough-and-ready fashion of the Edinburgh school, without mishap or alarm, in my subsequent laboratory experience I frequently lost animals by overdose of chloroform, and for a time I took to ether instead.

From this I was led to make a long series of experiments on isolated nerve with ether and with chloroform vapours at all kinds of percentages in air. Using the excitability of nerve as my touchstone, I found that 10 per cent. chloroform vapour was immediately and irremediably fatal, while ether vapour at much higher percentage caused complete but only temporary inexcitability. I studied in the same way many other anæsthetic drugs—the chloromethanes and chloroethanes especially, and chloroform itself at percentages from 0·5 to 5 per cent. I came to the conclusion that chloroform is physiologically seven times as powerful as ether, that as a certain and controllable anæsthetic, chloroform is the best of the chloromethanes, and preferable to any of the various chloroethanes that have been recommended from time to time for clinical use, but that the safe administration of chloroform requires the continuous and uniform inhalation of chloroform and air at between 1 and 2 per cent.—or, as I then expressed it for the sake of emphasis, "not below 1 per cent., not above 2 per cent."

In the discussion that took place on the communication of these results at the meeting of the British Medical Association at Montreal[1] (1897) and in the following year at the Society of Anæsthetists, the principal points of opinion elicited were to the effect that it was certainly desirable that chloroform should

[1] Waller: "The Action of Anæsthetics on Nerve; Ether and Chloroform," *Brit. Med. Journ.*, November 20, 1897.

Waller: "On the Dosage of Chloroform," *Brit. Med. Journ.*, April 23, 1898.

Waller: "On the Administration of Chloroform to Man and to the Higher Animals," *Lancet*, November 28, 1903.

Waller: "On the Physical Relation of Chloroform to Blood," *Proceedings of the Royal Society*, Vol. 74, 1904, p. 55.

Waller and Geets: "The Rapid Estimation of Chloroform Vapour," *Brit. Med. Journ.*, June 20, 1903.

Waller: "Chloroform Estimation by Densimetry": "Ether Estimation by Densimetry," *Proceedings Physiological Society*, July 11, 1903.

Waller and Collingwood: "Estimation of Inspired and Expired Chloroform," *Proceedings Physiological Society*, February 25, 1905.

Waller: "A Physiological Contribution to the Problem of Chloroform Anæsthesia," *Brit. Med. Journ.*, December 24, 1904.

Waller: "On the Action of Anæsthetics," Presidential address to the Physiological Section of the British Association, Leicester, 1907.

be administered with plenty of air, but that it was practically very difficult if not impossible to secure the administration of the vapour between any definite limits of percentage.

This opinion was, I think, in the main correct. Snow's inhaler, in which the patient inspired through a bottle containing liquid chloroform, had been found to be not free from danger, the *estimated* percentage was rather high (4 per cent. or 5 per cent.) and the apparatus fell into disuse until recently, when it was revived under a slightly different form by Vernon-Harcourt, and favourably reported on by a committee of the British Medical Association.[1] The percentage of delivery of this modified form is adjusted to be from 0·5 to 2 per cent., but in my opinion the percentage scale with which the instrument is furnished is no real indication of the actual percentage of delivery. The method is the everyday method of the laboratory, where prompt rather than safe anæsthesia is required; but obtained at a price of accidental deaths by overdoses with which every physiologist is familiar.

Paul Bert's method to deliver to the patient chloroform and air at known percentage from a large gasometer proved to be quite impracticable.

Another French apparatus, that of Raphael Dubois, has fallen out of use in France, and has been condemned in this country as being cumbrous and expensive. It is, as I have elsewhere stated,[2] a very safe apparatus indeed, and my opinion has been confirmed during the last three years by the far more extensive experience of Dr. Paul Chapman, of Hereford. I believe, however, that the method is inferior both in certainty and in convenience to that which I shall finally describe.

An apparatus of my own,[3] called the wick-vaporiser, based on the principle of the carburettor of a motor-car, and adjusted to deliver by the evaporation of chloroform from 1, 2, or 3 wicks, 1, 2, or 3 per cent. of chloroform vapour, has rendered good service in the laboratory, has proved satisfactory in a limited number of trials in hospital, but is open to an objection that applies in more or less degree to all other forms of apparatus

[1] *Brit. Med. Journ.*, July 1903.

[2] "An Examination of Apparatus proposed for the Quantitative Administration of Chloroform," *Lancet*, July 9, 1904.

[3] "The Wick-Vaporiser," *Proceedings of the Physiological Society*, August 19, 1904; *Journal of Physiology*, vol. xxxi.

I have examined: viz. the graduation, however carefully made in the laboratory, is illusory when copied by the instrument-maker, and still more illusory in the hands of an anæsthetist.

The Roth-Dräger apparatus is designed to supply a mixture consisting of a measured volume of oxygen and a measured volume of chloroform vapour from a measured number of drops of liquid chloroform. The apparatus has been used largely in Germany during the last four or five years. I tested it in 1904, and found that the delivery is approximately in accordance with the graduation of the scale. The apparatus is, however, cumbersome and complicated, more so than the Dubois.

But I do not propose to encumber these pages with the detailed description of particular apparatus. All I wish to do is to make good the point that the necessity of measurement has given rise to measuring apparatus in France, in England, and in Germany. All such apparatus applies one or other of two principles—the chloroform mixture being supplied to the patient on the vacuum system—Snow, Vernon-Harcourt; or on the plenum system—Dubois, Junker, Waller, Roth-Dräger. On the vacuum system, the patient inspires air through a vessel containing liquid chloroform by a broad inlet tube and a closely fitting face-piece. On the plenum system the patient inspires from a freely open face-piece in which an excess of chloroform and air of required percentage is maintained by a pump. Obviously the former method is more difficult to apply perfectly than the latter.

The most serious objection to every sort of graduated apparatus is, however, the fact that the graduation, valid in the laboratory to an error of perhaps 10 per cent., is liable to variations of 100 or 200 per cent. in hospital use. The value of any scale of any sort of graduated apparatus used under clinical conditions is less than none, for the graduation is misleading. Variations of temperature, of ventilation, agitation, etc., may at once cause the unit percentage to rise to 2 or 3, or to fall to ½ or less, and the scale becomes completely misleading—1 may mean 2 or 0·5; 2 may mean 4 or 1; 0·5 may mean 1 or 0·25—and any discussion as to what percentages are safe or dangerous is waste of time. Indeed, when one asks by what methods percentages are determined, he must marvel at the facility with which it has become customary for anæsthetists to talk about this or that percentage

of chloroform. All the same, this loose talk in terms of percentage is a considerable step in advance of the state of matters a few years ago, when anæsthetists were accustomed to scout the possibility of any sort of measurement, and to judge of the action of chloroform solely by its result upon the patient. Obviously, under such conditions, the only safe anæsthetist was the experienced anæsthetist, the man who had learned to recognise danger as soon as danger became visible. No man can be thus experienced from the outset, some men become thus experienced more rapidly than others, others never become thus experienced. Is it not, therefore, self-evident that in every few thousand administrations there must be cases of serious danger or death, and that in every single administration there must be anxiety or alarm? And may it not be expected of science, which is measurement, that the heavy price of anæsthesia should be reduced? I assert again what I have already asserted repeatedly in medical circles—at Montreal before the British Medical Association, at the Society of Anæsthetists in London in 1898, at Johannesburg to the Physiological Section of the British Association in 1905, in many communications to the *British Medical Journal* and *Lancet*—that the price need not be paid, or, at least, may be greatly reduced, by the application to medical practice of two or three simple lessons of arithmetic learned in the physiological laboratory.

It was estimated by Snow[1] that 18 minims of chloroform in the blood of a patient will produce anæsthesia, and that double the amount is fatal.

Gréhant estimated that the blood of animals killed by chloroform inhalation contained about 50 milligrammes per 100 grammes.[2] This proportion would be about $2\frac{1}{2}$ grammes in the blood of an average person.

Buckmaster and Gardner[3], by a more precise method, arrived at an almost identical result. The amount of chloroform in the blood of an animal killed by inhalation of strong vapour was from 40 to 60 milligrammes per 100 grammes; that in the blood

[1] Snow, *On Chloroform and other Anæsthetics*, 1858. 18 minims is approximately 1 c.c. of liquid chloroform, or 300 c.c. of chloroform vapour. 1 gramme of liquid chloroform gives approximately 200 c.c. of vapour.

[2] Gréhant et Quinquaud, "Dosage du Chloroforme dans le Sang d'un Animal anesthésié," *Comptes Rendus de l'Académie des Sciences*, xcvii. 1883, p. 753.

[3] Buckmaster and Gardner, "The Estimation of Chloroform in the Blood of Anæsthetised Animals," *Proceedings of the Royal Society*, vol. 79, 1907, p. 309.

of an animal completely anæsthetised was 20 to 40 milligrammes. And following out the percentage in the course of anæsthesia, they called attention to the fact that at the very outset the percentage commonly reaches a maximum value within the first minute or two, and thus gives rise to "a first danger point" during the induction of anæsthesia.

As ordinarily administered, it is quite possible that a patient should take into the lungs in one minute 10 litres of air, containing 4 per cent. of chloroform vapour, *i.e.* 400 c.c., of which one-half may be at once absorbed by the pulmonary blood and carried to the heart, *i.e.* 200 c.c. or 1 gramme, or one-half the quantity reputed to be lethal. Merely by a single deep gasp after the breath has been held, it would be quite possible for a patient to take suddenly into his lungs perhaps 100 c.c. of vapour, or half a gramme of liquid chloroform. Is it to be wondered at that a heavy price is paid for the boon of anæsthesia? Is it not, rather, matter for surprise that the price is not heavier than it is?

The principal condition upon which the required state of anæsthesia depends is the mass of chloroform present in the inspired air, or, in other words, on the tension of chloroform vapour in the lungs. And it is important that, as far as possible, the percentage (or tension) of chloroform vapour in the inspired air should be kept as constant as possible by the continuous administration of chloroform at low percentage. The intermittent and irregular administration at high percentage should, as far as possible, be avoided. In comparison with the fulfilment of this principal condition all other considerations are of subordinate importance—the fact that the administration should be commenced at relatively low percentage, and once anæsthesia is induced that it can be maintained at low percentage; the fact that patients differ in their susceptibility to anæsthetics; the fact that more or less profound anæsthesia is required, according to circumstances; and many other detailed facts, to the scientific control of which it is primary that we should know how much chloroform is actually delivered to the inspiration of the patient, or, rather, what is the actual percentage and tension of chloroform vapour in the inspired air.

Some ten years ago I said that the percentage should be between 1 and 2. During the last few years I have elaborated a ready method of estimating that percentage, and have

attempted to devise a ready method of delivering chloroform vapour and air between the required limits.

I have at last hit upon a combined method of estimation and of delivery that has proved itself to be an admirable laboratory method, and that will, I believe, prove to be of great service as a hospital method of exact administration.

The arithmetical data upon which the method depends are as follows:

A litre of chloroform vapour weighs .	5·3	grammes
„ air „ „ .	1·3	„
Difference	4·0	„
Or difference per 1 c.c. .	4·0	milligrammes

A litre of chloroform and air at 1 per cent., or 990 c.c. of air + 10 c.c. $CHCl_3$, weighs 1·34 grammes, and every 40 milligrammes of weight in a litre flask or bulb of mixture indicates 1 per cent. of chloroform vapour in the mixture—or in a 250 c.c. bulb each centigramme indicates 1 per cent. This affords a ready means of estimating from time to time the percentage of chloroform vapour in mixtures of chloroform and air, and I have used it extensively as a means of calibration and control of apparatus. But, obviously, it is not a method for use outside the laboratory.

But the next step, by which I sought to obtain for the laboratory a means of estimating from moment to moment, and recording, the fluctuations of percentage taking place in the chloroform mixture delivered to an animal, and of varying the percentage as desired for the experiment, put me in possession of an instrument which at once fulfilled its laboratory purpose and at the same time is obviously capable of being transferred to the operating theatre.

Instead of weighing in air a bulb full of chloroform mixture, I weighed, or rather counterpoised, a bulb full of air in a jar traversed by the chloroform mixture; the bulb, of course, rose and fell as the mixture was made more or less dense by more or less chloroform vapour. The pointer of the balance was then graduated in chloroform percentages by appropriate weights—increments of 40, 80, 120 milligrammes for 1, 2, and 3 per cent. $CHCl_3$ with a litre bulb.[1] A light pen fixed to the beam of the

[1] I have not talked about temperature and pressure corrections, which should be taken into account when required, and ignored when not required. For

balance and a smoked cylinder served to give a record of the rise and fall of the bulb with rise and fall of chloroform percentage, and incidentally served the useful purpose of damping the oscillations of the beam and pointer. In order to avoid accidental fluctuations of the percentage delivered to the animal, it was advisable to use a vessel of considerable volume containing the mixture on its way to the animal. I used the case of the balance for this purpose. Air was pumped into it through or over the surface of chloroform by the ordinary respiration pump or by a bellows, and went on by a second tube to the tracheal cannula or mask. The large capacity of the balance case—in this case 30 litres—proved to be suitable for the induction of anæsthesia and for its safe gradual modification. The chloroform percentage rose from zero to 2 per cent. in about two minutes; the lag of voluntary diminution and increase was about ten seconds; the pointer could at will be kept perfectly steady at any desired percentage. Finally, I may remark that for all ordinary purposes of the laboratory a comparatively coarse balance is best adapted. In the apparatus now in daily use the graduation is from 1 to 3 per cent., which gives records of 6, 12, and 18 mm. amplitude.

Judging by the comments of visitors to the University of London, acquainted with the various haphazard methods in use for producing and maintaining anæsthesia of the human subject, and witnessing for the first time the ordinary procedure followed in the physiological laboratory for the producing and maintaining of anæsthesia of animals, the usual thought aroused seems to be one of regret that the human subject cannot be anæsthetised with similar uniformity and safety.

My own feeling is one of intense surprise, that the clear practical experience of the laboratory should be of so little use to the medical profession, and that year by year the death-roll of chloroform anæsthesia should continue undiminished.

Occasional attempts have indeed been made in France, in Germany and in England, to bring graduated apparatus into use, and have met with a certain amount of success in the

ordinary temperatures (18° C.) and pressure (760 mm. Hg) a bulb of 1054 c.c. would be required for these increments. Or if, as was the case of the particular balance now in my hands, the bulb had a capacity of 870 c.c., the counterpoising weights for 1, 2, 3 per cent., should be taken as 33, 66, and 99 milligrammes.

hands of a few anæsthetists. But for one reason or another, graduated apparatus has not met with general favour; instruments have been too dear, or too troublesome, or have failed to fulfil the promise of their inventors and advertisers. Each inventor, whether French or English or German, has had his instrument patented; and the consequence has been that each instrument has been advertised as perfect, whereas as a matter of fact no instrument can be perfect—every instrument requires to be used intelligently.

I think it may be useful to describe the ordinary daily practice of this laboratory towards animals, and to indicate as briefly as possible how I should propose that a similar procedure should be applied to hospital anæsthesia. And I shall at once premise, in reply to the inevitable objection that the method is too troublesome for hospital use, (1) that it is not too troublesome for daily use in the laboratory for animals, (2) that several thousand animals have been anæsthetised in this laboratory during the last five years, without the accidental loss of a single animal, and (3) that, even admitting that the procedure is more troublesome than the ordinary practice, it is not unreasonable to expect as much trouble to be bestowed upon the safe anæsthesia of a patient in a hospital as is bestowed upon an animal in a laboratory. In point of fact, the trouble of application would be smaller in the case of man than it is in that of an animal.

The procedure in this laboratory as regards animals is as follows:

First step.—The animal is placed in a closed glass chamber (a large bell-jar, or a small cupboard with plate-glass front), into which chloroform-and-air of desired percentage is pumped. The latter is provided by pumping air by a small electric motor through an ordinary wide-mouthed bottle containing liquid chloroform, into a large-mixing chamber (capacity = about 30 litres), containing the chloroform balance and provided with an inlet from the chloroform bottle and an outlet to the animal chamber. The flow of air is rendered uniform and of suitable volume per minute by means of an elastic reservoir and a perforated stop on the course of the supply tube. The percentage of the mixture administered is watched on the pointer scale (and if desired recorded by a light pen). It is regulated by varying the depth of a tube in the chloroform bottle and by

admitting more air to the mixing chamber. In general, anæsthesia is induced by chloroform and air at 2 per cent., and the animal is kept under anæsthesia at 1 per cent. until required.

Second step.—The anæsthetised animal is removed from the bell-jar or cupboard, for the operation of tracheotomy. The outlet tube of the mixing chamber is attached to the tracheal tube, and anæsthesia is maintained by a mixture at between

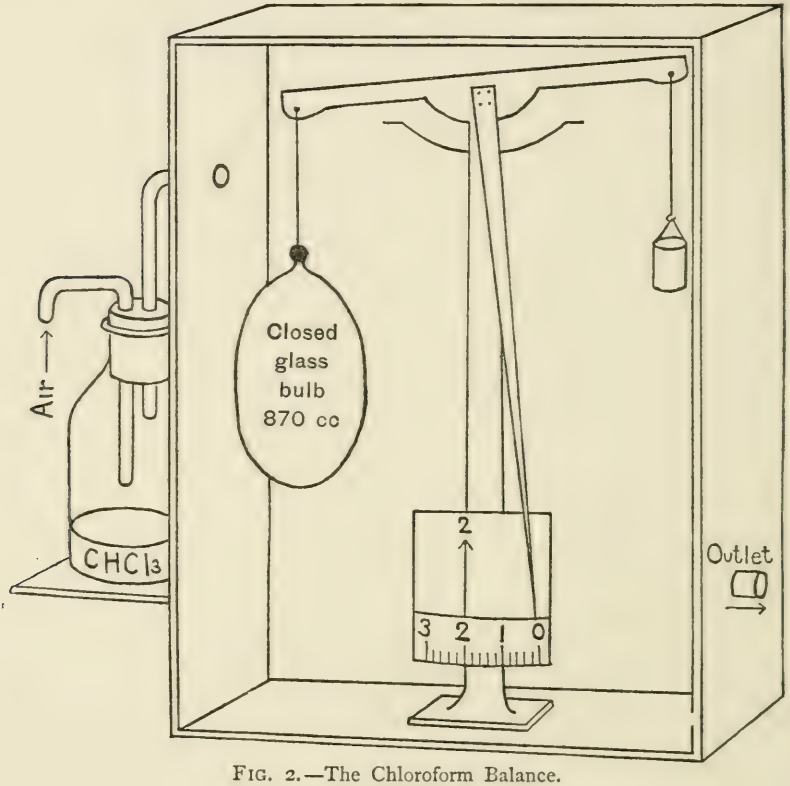


FIG. 2.—The Chloroform Balance.

1 and 2 per cent., as shown by the index of the chloroform balance. The chloroform-and-air is taken by the animal by its ordinary respiration, or supplied to the animal by the action of the pump (in which case the elastic bag and perforated stop are removed from the supply tube). In either case the anæsthetic vapour is under slight positive pressure—*i.e.* it is delivered on the plenum system.

The *procedure in hospital* is (or would be) simplified by the fact that the first step necessary in the case of animals, viz. anæsthesia in a confined space, is not necessary for the human subject. Obviously, also, tracheotomy is omitted; all that is required for the human subject is an open mask or face-piece at the end of the delivery tube. For since the delivery of chloroform to the patient is on the plenum principle, and such pressure as exists in the mixing chamber and delivery tube is positive, length of tube is immaterial, and does not place any extra work upon inspiration by the patient. All the apparatus required by the anæsthetist at the operating-table consists of the tube itself, and the face-piece or other terminal contrivance; the pump, the chloroform bottle, the mixing chamber, and the chloroform balance are at a distance from the operating-table, out of the way, but not out of sight. The size of the mixing chamber (30 litres) ensures the continuous and uniform supply to the patient of chloroform (or ether) vapour at known and visible dilution. The indication of percentage is easily verified, and is visible to all persons present. The concentration, which, by reason of cooling of the chloroform, automatically remains below 3 per cent., can be varied at will with sufficient rapidity, as shown by the indicator, and it cannot be suddenly augmented to a dangerous amount. The attention of the anæsthetist is free to be wholly bestowed upon the state of the patient, in accordance with which the strength of vapour is raised or lowered, and *seen* to be raised or lowered. (At the cost of a very trifling additional trouble, a permanent record can be taken of the strength of vapour employed during the whole time of its administration.)

The apparatus in its laboratory form is not very portable. And although, no doubt, it may be practicable to render it more portable, I prefer at present to keep to the dimensions with which I am familiar, and to advise its use chiefly as a hospital fixture, set up in the operating theatre and in the room or rooms in which patients are prepared for operation. I am convinced that an installation of apparatus of this character would go far to remove the possibility of prolonged series of fatalities such as that mentioned in the footnote to p. 612, and to allay an incalculable amount of anxiety in the minds of all those who know. And as regards the general public, who at present do not know, I am convinced that if the serious

misfortune of an unreasoning dread of anæsthetics is to be avoided, the danger of anæsthesia must be reduced to whatever may be its unavoidable minimum, by applying in the hospital the clear teaching of the laboratory.

A direct indicator of the percentage of chloroform in the air delivered to the inspiration of a patient is, in my opinion, a valuable safeguard. It is not difficult to secure; it is legible at a glance. I do not say that its use would abolish all danger, but I do assert that the common knowledge of the physiological arithmetic of chloroform would go far to diminish the excessive price of anæsthesia.

RECENT RESEARCHES ON CHLOROFORM ANÆSTHESIA

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Any one who at the present time reflects upon the advances which have taken place in medical practice within the last twenty-five years will easily recognise that the introduction of antiseptic and aseptic methods—for which all mankind is under a lasting debt to Lord Lister—has largely increased the frequency of surgical operations. The frequency with which general anæsthetics are employed has consequently also augmented to an equal or even greater extent, and it may be admitted that the safe administration of such a drug as chloroform is to a large extent dependent upon the skill of the individual anæsthetist. However, deaths may, and do, occur during anæsthesia. Life may be lost before an operation has been commenced, and the cause or causes of such an accident has been the subject of much useless speculation, and also of some valuable experimental work on the physiology of anæsthesia. The whole science and art of medicine advances sometimes at a slow, sometimes at a quicker rate, but any given degree of progress is almost entirely regulated by those additions to knowledge which are founded upon exact experiments carried out in laboratories.

During the past few years the subject of anæsthesia by

chloroform has been under the consideration of a special committee appointed by the British Medical Association.[1] The experimental work thus initiated has proved of much service, especially in indicating the limit-value of the chloroform vapour which can be safely inhaled. The introduction of an inhaler by Vernon Harcourt for the administration of chloroform with safety is also the direct outcome of this work. The simplest and quickest way to determine the percentage of chloroform vapour in air is by a method suggested by Waller,[2] which depends upon the proportional increase in weight which known volumes of air and chloroform exhibit, compared with the same volume of air. The purpose of this paper, however, is to draw attention to recent work on chloroform anæsthesia which has been carried out in this country and in France. The activity of observers in Germany has not been directed to this particular inquiry.

Besides chloroform, some hundreds of substances have been shown to possess in different degrees well-marked anæsthetic and narcotic properties. All forms of life, the simplest and the most complicated, unicellular and multicellular organisms, can be shown to exhibit very similar phenomena in response to minute, moderate, and toxic doses of those drugs which are grouped as anæsthetics; and it is probable some single fundamental type of interaction which takes place between the anæsthetic and the protoplasm or bioplasm of cells, will be found to take place, and that upon this fact a rational explanation of the anæsthetic process will be given. The condition finally established by increasing any given anæsthetic is one of profound intoxication, and a state of narcosis is induced in the higher animals, owing to the successive interference with the excitability of the cortex of the brain, of the grey matter of the spinal cord, and of the grey matter of the spinal bulb or medulla oblongata. These parts of the central nervous system become inactive, and a progressive paralysis of the nerve cells becomes established, in which the sensory and receptive apparatus is probably impaired before the motor. It is beyond dispute, as any one must admit who is familiar with the subject, that the anæsthetic state is a condition where

[1] *British Med. Journal*, July 12, 1902, July 18, 1903, July 23, 1904, July 22, 1905, July 14, 1906.

[2] Waller, *Proc. Physiological Soc.* 1903.

the tissue elements, or cells of the body, are poisoned in different degrees, and the cells of the central nervous system in higher animals exhibit a peculiar elective or selective power in picking up such a drug as chloroform, compared with other portions of the excitable tissues or neuro-muscular apparatus of the body. No matter by what particular hypothesis this selective power is explained, it is equally certain that chloroform does not actually accumulate in the tissues, or remain permanently held by protoplasm, for a restitution of the normal functions of the whole body is always to be seen, provided that the interference with function has not been of too long a duration.

As an explanation of the anæsthetic state some observers on insufficient grounds have attributed this to a local anæmia of the cerebral cortex. But it is known that this view is not in accord with experimental evidence, for the opposite occurs in the early stages of chloroform narcosis; and as Roy and Sherrington and also Hürthle have demonstrated, the blood-flow through the brain is actually increased. In profound anæsthesia, the bulbar centres—those complex nerve-cell aggregations which physiologists speak of as the vaso-motor centres, which control the bore of the smallest arteries, so that these are in no sense inert tubes of constant diameter, the respiratory centres controlling the muscular movements of the thorax, and the cardiac nerve-centres, which govern the liberation of energy by the heart muscle—become paralysed. Frequently these centres are finally poisoned in the order in which they have just been mentioned, and then, owing to a vaso-motor paralysis, which is particularly a feature of chloroform poisoning, such a quantity of blood may accumulate in the dilated blood-vessels that a true cerebral anæmia may occur. Here it may be mentioned that experiments upon animals have yielded incontestable evidence that among mammals the vaso-motor nervous mechanism is more perfectly developed in a physiological sense in man than in the apes, in the apes than in the carnivora, in these more than in rodents. As Leonard Hill[1] has shown, the explanation of this perfected mechanism in man is related to his erect posture, and the circulation of blood through the brain is maintained at a normal value, whether an animal is placed in a horizontal position or in the feet-down or head-down position.

[1] *Journal of Physiology*, vol. xviii. 1895.

From two volumes published last year by a well-known anæsthetist[1] on the chloroform problem, a few remarks may be abstracted, in order to show how the phenomena witnessed in chloroform anæsthesia may lead a skilled clinical observer to views for which at present there is no sufficient experimental evidence, though it is impossible for any one to deny that the deprivation of oxygen may play a very important part in throwing the cells of the neuro-muscular apparatus out of action. The author considers that "chloroform and ether are typical examples of a group of agents which possess the power of abstracting oxygen (from the blood) without otherwise injuring the blood."[2] Again, "all narcotic agents are oxidisable, and cause all their results (direct and indirect) by abstracting oxygen from the blood."[3] "They do not act directly upon the cerebral centres, but indirectly through the intermediation of the -oxy factor, which it would appear is the only known cause of the suspension of their functions."[4] Further, he states that "it is impossible for chloroform to remain in the blood without becoming oxidised; but if there be an excess in the circulation, *i.e.* such an amount as will require more for its oxidation than can be supplied by blood, what influence does the rest exert?"[5] The purpose of this article is not to criticise the views held by any one; but the ideas put forward in this way, supported as they are by no sufficient evidence, are in absolute contradiction to a knowledge which has been most slowly built up by experimental methods. All the evidence acquired by experiments to determine this particular fact, whether any oxidation processes whatever are possible within the blood-stream, has uniformly shown that no measurable consumption of oxygen under any circumstances, even by a substance so easily oxidisable as pyrogallic acid, can be detected with certainty while the blood is within the vessels. It is a cardinal fact, and one accepted by every physiologist, that the consumption occurs within the tissue cells of the body, and that this is dependent entirely, not upon the supply of oxygen, but upon the requirements of the entire organism. The evidence for this is to be found in any physiological text-book. For example, Schmiedeberg found that such easily oxidisable

[1] *The $CHCl_3$-problem*, by Richard Gill. 2 vols. 1906.
[2] Vol. ii. p. 275.
[3] Vol. ii. p. 278.
[4] Vol. ii. p. 279.
[5] Vol. ii. p. 267.

substances as benzyl alcohol or salicylic aldehyde undergo no change within the blood-stream; but that the substances are easily oxidised to benzoic acid and salicylic acid when the blood-flow passes among the cells of the kidney.

The explanation which is advanced—that anæsthesia is due to the abstraction of oxygen by chloroform—rests on no certain basis, for it is quite easy to anæsthetise a frog when all its blood is replaced by ·65 per cent. sodium chloride. Moreover, all animals, including man, who live at varying altitudes from the sea-level to 10,000 ft., are luxuriously supplied with oxygen, so that the amount available far exceeds the need. As will be shown subsequently, the actual amount of chloroform in the blood during anæsthesia is known, and assuming, which is not the case, that it is easily oxidised, the amount of oxygen which might be abstracted in this way would not produce any symptoms at all, except in so far as the oxidation products could exert an effect, and still less possible would it be for a state of anæsthesia to be established by so small a diminution in the oxygen-content of the blood. The destiny of the chloroform in the blood is to be exhaled; and if any amount of it is oxidised this takes place, not in the blood, but in the tissues of the body. Kast [1] and Zeller,[2] also W. H. Thompson,[3] have found an excess of chlorides in the urine after chloroform narcosis; while some observers—Wagener,[4] Thiem and Fischer [5]—state that chloroform as such can be recognised in the urine. An excess of chlorides is not conclusive evidence that the drug is oxidised, for these are increased, but not to the same extent, after anæsthesia by ether.

Experimental evidence that chloroform may be decomposed within the organism has been furnished by Desgrez and Nicloux,[6] who found small quantities of a combustible gas which might be hydrogen methane or carbonic oxide in normal blood. 1000 cc. of this yielded 1·2 cc. of a gas which was apparently carbonic oxide. In the same quantity of blood from animals deeply chloroformed larger amounts were found—in one case 6·9 cc. of carbonic oxide. This increased amount was

[1] *Zeitschr. f. physiolog. Chemie*, xi. 1887, and *Jahresber. f. Tierchemie*, xviii. 1888.
[2] *Zeitschrift f. physiolog. Chemie*, viii. 1883.
[3] *Proc. of Physiological Soc.*, January 21, 1905.
[4] *Jahresbericht f. Tierchemie*, xxx. 1900.
[5] *Chem. Zentralblatt*, i. 1890.
[6] *Arch. de Physiologie*, No. 2, 1898.

believed to arise from a decomposition of chloroform. These observations have neither been confirmed nor refuted, but in any case the amount of the drug which was decomposed would be small.

The most varied types of living animal and vegetable cells respond in an identical manner to the action of chloroform, a drug which is seven to eight times as toxic as ether (Waller). Exceedingly minute doses stimulate living protoplasm; thus, the time of inflorescence of the lilac or azalea is quickened by chloroform vapour.[1] With progressively increasing amounts of the drug, the energy discharges of any organism decrease, and finally disappear with a lethal amount. Both individual cells and organisms differ in the degree of their reaction to anæsthetics; but with a sufficient concentration of the drug, the final result is death. Experiments have shown that dogs and other animals are effectually killed by amounts of chloroform which are incapable of producing anæsthesia—in other words, the metabolic or nutritional processes of the body are profoundly affected, the temperature falls, and death occurs. This phenomenon was clearly described by Paul Bert[2] in 1883, and has been more recently studied by B. J. Collingwood.[3] The following table is constructed from experiments carried out on dogs by Paul Bert:

Percentage of chloroform vapour in air.	Results.	Hours from commencement of administration till death.
·8	No anæsthesia	9–10
1·2	Diminished sensibility	6–7
1·6	Anæsthesia slowly induced	4
2·	Anæsthesia in a few minutes	2–3
2·4	„ „ „	1·7
3·	„ „ „	·66
4·	„ „ „	·5
6·	„ „ „	·005

It will be seen that the toxic action of chloroform profoundly checks the nutritional or metabolic phenomena of the body; when a low percentage is inhaled an enormous quantity of chloroform can pass into and out of the body without producing

[1] E. Lemoine, *Jour. of Royal Hort. Soc.* October 1903, and Leblanc, *Soc. Cent. d'Hort. de Nancy*, 1906.

[2] *Comptes rendus de l'Acad. d. Sc.*, t. xcvi. p. 1831, 1883.

[3] SCIENCE PROGRESS, vol. i. p. 12.

any obvious effect except a fall in temperature. In this its action closely resembles alcohol, which has been shown by Tarchanoff to impede growth and check the development of the excitable sensori-motor regions of the cortex of the brain. Chloroform also appears to exert a marked influence on the growth of animals. Experiments have been carried out for a period of five months on kittens from the same litter and of equal vigour, which show that there is a retardation of growth, estimated by weighing, in young animals which were anæsthetised up to the point at which the corneal reflex just disappeared, twice a day. Animals, however, like plants, exhibit increased metabolic activity subsequent to this treatment, and their rate of growth more than compensates for the retardation.[1]

The Relations which may exist between Chloroform and Blood

It has already been stated that the condition of anæsthesia can be induced in isolated cells or in organisms which possess neither a blood system nor a nervous system. The condition can be established in any living thing, no matter how low or how high may be its organisation. How the anæsthetic state is actually produced is at present unknown, though the theory advocated by Hans Meyer[2] and Overton[3] is generally accepted as affording some sort of explanation. These observers, independently and almost simultaneously, ascribed the action of such an anæsthetic as chloroform to the fact that certain cell-constituents, such as lecithin or cholesterin, were capable of physically taking up or absorbing the anæsthetic. When this has occurred the activities of the cell are interfered with, especially in the sense that its response to excitation is diminished. The greater sensitiveness of the central nervous system, compared with other organs of the body, such as the muscles, is considered to be explained by this hypothesis, since the former is peculiarly rich in bodies, or lipoids, which are soluble in chloroform, or the same idea may be expressed by regarding lipoids as cell-constituents which pick up anæsthetics which are soluble in these. The basis for the theory

[1] Shapiro, *Proc. Physiolog. Soc.* December 10, 1905.
[2] *Archiv f. exp. Pathol. u. Pharmakol.* xlii. 1899, and xlvi. 1901.
[3] *Studien über Narkose*, Jena, 1901.

which has just been indicated rests largely upon physical experiments as to the relative solubility of anæsthetic substances in water and in olive oil. It is true that many anæsthetics, chloroform among them, are soluble in all proportions in oil, while water takes up only ·72 per cent.; but a convincing explanation of what occurs in anæsthesia is not likely to be gained by studies of this nature, no matter how accurately they are carried out; and, moreover, they will not afford an explanation of the action of such narcotics as morphia or conia. For these Overton, to whom we owe the introduction of the term "lipoid," suggests the existence of combinations between the drug and cell-protoplasm, a view which Benjamin Moore and H. E. Roaf have particularly put forward as a possible explanation for the action of all anæsthetic substances. Some of these, such as chloroform, may form easily assimilable and dissociable compounds with the living protoplasm; others, such as morphia, may form more stable compounds, and will therefore probably be more specific in their action.

The attention of Benjamin Moore and H. E. Roaf was first attracted to the subject of anæsthesia by witnessing some experiments performed by C. S. Sherrington and S. C. M. Sowton. If a mammal be killed and the heart removed, this organ can be shown to beat regularly for more than four days if it is supplied with a weak, watery solution of certain inorganic salts, provided that the liquid is saturated with oxygen gas. The heart, therefore, will exhibit a prolonged period of activity outside the body when there is no blood supplied to the organ. This demonstration we owe to F. S. Locke.[1] A concentration of chloroform, added to the liquid which feeds the heart, of 1 in 100,000, produces a constant effect; the vigour of each individual heart-beat is diminished. This effect rapidly appears, and persists for just as long as chloroform of this low but adequate concentration is bathing the interior of the heart. When the solution containing chloroform is replaced with Locke's fluid, the effect on the heart's beat disappears and the contractions regain their normal vigour, to again sink when the weak chloroform solution is substituted. From this experiment, to quote Moore and Roaf, it was clear that chloroform exerted no cumulative action on the living protoplasm of muscle; that is to say, the effect on the cardiac beat was the

[1] *Zentralbl. f. Physiol.* December 30, 1905.

reduction in vigour to a certain extent and no more. No matter how prolonged was the passage of the chloroform solution, the effect rapidly disappeared when the anæsthetic was removed. Secondly, the effect upon the living cells of the heart muscle depended solely upon the concentration (solution tension or osmotic pressure) of the chloroform in the cell for the time being; and, lastly, the effect at any moment was not at all due to the total amount of chloroform which had been supplied to the heart up to that particular time. Experiments of this nature suggested the view that the effect might be due to some unstable association or combination between the anæsthetic and the cell protoplasm of muscle, and that this existed for only so long as the pressure of the anæsthetic was maintained. Diminish this pressure to zero and complete recovery takes place, the association ceasing to exist; re-establish the pressure and the effect of the anæsthetic once more is witnessed. In the opinion of the writer no other view than this is possible. The condition of chloroform anæsthesia in man can be most satisfactorily comprehended by considering that from the commencement of the inhalation of an air-and-chloroform mixture the pressure of the anæsthetic augments in the blood, and it is this pressure which first of all forces the drug into the lymph and then into the cells of the body, some of these being more permeable and therefore more susceptible than others; the degree of anæsthetisation of the cells being due not so much to the absolute quantity of chloroform supplied, as to the maintenance of a definite pressure of the anæsthetic in the blood. From a large number of experiments which the writer has witnessed, it is clear that no definite fixed relation exists between the proportion of chloroform in the blood and the effect of the drug, for this is determined not by the absolute amount which is held, but by the actual quantity which passes into the cells of the central nervous system, so that the control of these over the liberation of energy by the organism is reduced to a minimum.

Since in the higher animals arterial blood is the vehicle by which chloroform is taken up from the surrounding medium and a certain solution pressure of the drug must be attained before anæsthesia occurs, the relations which may exist between blood and chloroform have been the subject of much investigation. The proteins of the blood, both those in the plasma and

the red corpuscles, particularly hæmoglobin, have been proved to form definite unstable compounds or physical aggregations with chloroform; and the position taken by the anæsthetic in hæmoglobin is not that of the respiratory oxygen, for the oxygen-carrying power of this protein is in no way impaired or interfered with by the presence of chloroform, though it is quite certain that during narcosis with chloroform arterial blood becomes progressively richer in reduced hæmoglobin. Evidence for the above statements was first given by Benjamin Moore and Roaf,[1] though numerous other observers, such as Pohl, Waller, Wells, and Vernon Harcourt, among others, had recognised with what tenacity chloroform is held by the blood after anæsthetisation, and how difficult it was to recover the drug; so that while the gases of the blood can be evacuated, only ·014 gramme out of ·108 gramme of chloroform in the blood can, as Waller demonstrated, be recovered.[2]

The effect of adding chloroform to blood *in vitro* was described by Preyer in 1871.[3] Formánek[4] more minutely investigated this subject, and proved that when a solution of hæmoglobin was treated with chloroform and kept at a temperature of 50°–53°C. for some time, the protein was so completely precipitated that the filtrate was free from hæmoglobin. Edie's experiments showed that precipitation occurred when the hæmoglobin solution contained from 1·5–7·5 per cent. of chloroform.[5] Even when the amount of hæmoglobin in solution varied and the percentages of chloroform added also varied, the percentage of the anæsthetic in the precipitate to the amount of hæmoglobin which was not precipitated remained constant, from which it may be inferred that the precipitate formed is of the nature of a definite chemical compound or, possibly, a definite physical aggregation.

Experiments *in vitro* have also shown that when a solution of hæmoglobin is taken, and 1 per cent. of liquid chloroform added, and the mixture shaken thoroughly, all the chloroform dissolves; no precipitate forms on standing either at the room or the body temperature. It must, of course, be remembered that experiments of this nature do not in any way imitate the conditions

[1] *Proc. Royal Soc.*, vol. lxxiii. May 1904, and vol. lxxvii. 1905.
[2] Waller, *Proc. Royal Soc.*, vol. lxxiv. June 9, 1904.
[3] *Die Blutkrystalle*, p. 104 : Jena, 1871.
[4] *Zeitschrift f. physiolog. Chemie*, vol. xxxi. 1900.
[5] Reports of Thompson Yates and Johnston Laboratories, Liverpool, vol. vi. 1905.

which occur when the vapour of chloroform is inhaled, and under no conceivable circumstances would anything like the amount of 1 per cent. of chloroform ever be found in the blood at the lethal stage of anæsthesia. In 1905 Friedrich Krüger again investigated this point.[1] He states that the precipitate described above is insoluble in water or neutral salt solutions, but is soluble in weak acids or alkalis; and from both of these the precipitate, as might have been expected, is again thrown down on neutralisation. The main interest of Krüger's work, however, lies in the fact that he has described and figured a special absorption spectrum for solutions of this precipitate; and should this observation be confirmed, it would undoubtedly greatly strengthen the views which are held by Moore and Roaf. Just as Edie has observed, so Krüger found that the chloroform-hæmoglobin precipitate was soluble in alkali; but whereas the former observer states that in solution in sodium carbonate yields the spectrum of alkaline hæmatin, Krüger describes the spectrum as one showing two bands, α and β, which occupy a position very similar to the well-known two-banded spectrum of oxy-hæmoglobin. The spectra are, however, dissimilar.

The difference between these and the effect of reducing agents can be seen from the following:

Spectrum.	Band α	Band β.	Effect of dilution with water.	Effect of reducing agents.
Hb + $CHCl_3$ Two bands α and β	Narrow	Broad intense	Disappear together or α before β	Reduced hæmoglobin and hæmochromogen
Hb + O Two bands α and β	Narrow intense	Broad	β disappears before α	Reduced hæmoglobin

Krüger considers that the effect of reducing agents justifies the conclusion that the chloroform-hæmoglobin precipitate consists of a mixture of hæmatin and hæmoglobin or methæmoglobin. Further, that the relation of chloroform to the blood-colouring matter is not that of an indifferent agent, which simply renders hæmoglobin insoluble, but that this substance is actually chemically changed, though he has not apparently considered the possibility that there might be a linkage between the drug and this protein. Formánek had already described the spectrum seen by Krüger as that of oxy-hæmoglobin, and for the present judgment may be suspended as to the exact

[1] *Hofmeister's Beiträge*, iii. p. 67, 1903.

spectroscopic characters of this body, especially as Krüger questions the accuracy of many of the existing charts of the spectra of the blood.

The facts upon which Moore and Roaf rely as proofs that a true compound or aggregation can, and actually does, take place between chloroform and cell-proteins have been elicited by several different methods which were employed for determining the maximum solubility of chloroform in water, salt solution (·75 per cent.), serum, hæmoglobin solutions, and in blood. The estimated maximum solubility at 13° C. by weight proved that chloroform has a much higher solubility in serum or hæmoglobin solutions than in saline or in water. For example, it was found that the following figures might be taken to represent the maximum solubilities:

	Per cent.
Water	·95
Saline (·75 per cent.)	·83
Serum	5·08–4
Hæmoglobin solutions or blood . . .	6

Determinations of the vapour pressure of chloroform in water, serum, and hæmoglobin solutions were also made with a specially constructed differential densimeter.

It is well known that of the three gases which exist in blood the amounts of oxygen and carbon-dioxide taken up are not proportional to the pressure exerted by these gases; in other words, their absorption does not follow the Dalton-Henry law. The question whether chloroform is or is not taken up by blood according to this law has never been experimentally tested. A given mixture of air and chloroform possesses a definite chloroform vapour pressure in the mixture. If such a mixture is inhaled, the vapour pressure of chloroform in air at the anæsthetising value is found to be about 8–10 mm. of mercury, which was the value observed by Paul Bert. The evidence given by B. Moore and Roaf, who have measured the vapour pressures of chloroform in water, serum, and hæmoglobin solutions of equal strength to that which exists in blood, indicates that the curves of pressures and concentrations in the case of serum and hæmoglobin are such that it is clear chloroform cannot be absorbed according to the Dalton-Henry law, but that the drug is actually associated with the blood-proteins

at certain vapour pressures, a fact which is not easy to determine except at high pressures. Conversely, the absorption of chloroform by saline does, as might be expected, follow the law of absorption for varying pressures, and when the results are plotted out the curve is a straight line. At a temperature of 40° C., and at the anæsthetising value of 8–10 mm. of mercury, the coefficient of distribution between vapour-space and solvent for hæmoglobin is about 7·1, and at a room temperature of about 15° C. this would be 18.

Additional experiments performed by Moore and Roaf render the views of Overton and Hans Meyer, which have obtained such wide credence, somewhat improbable. At equal concentration of chloroform in water and saline the vapour pressure of the drug always exceeds what is found for hæmoglobin or the protoplasmic cells of the heart, brain, or muscle; in other words, the association of the anæsthetic with proteins lowers the vapour pressure, just as the tension of oxygen in the blood is low, owing to its association with hæmoglobin. The theory which ascribes the action of general anæsthetics to a relationship which becomes established between the lipoids (substances of the cell soluble in ether, such as lecithin and cholesterin) does not conform with the experimental fact that ethereal emulsions of the brain, which organ is considered to be so specifically affected by chloroform, behave exactly like water or saline solutions; in other words, obey the Dalton-Henry law as far as chloroform vapour is concerned, while emulsions of the entire brain, cells and lipoids show that this law is no longer followed, but that there is undoubted association of the anæsthetic at high vapour pressures. Further, comparative determinations of vapour pressure and concentration of chloroform vapour leave no doubt but that it is the proteid constituent, and not the lipoid material, which is responsible for the actual physical aggregation or chemical combination which takes place. Far from the anæsthetic state being 'due to an affinity of the lipoids of the cells for an anæsthetic, the existence of such substances in bulk, as is the case for individuals who possess a large quantity of fat, actually imprisons a quantity of the anæsthetic which is given, so that it is no longer available for poisoning the cells of the organism, which is essential if anæsthesia is to occur, for it is well known to anæsthetists that the greater

the bulk of fat in a patient the greater will be the absolute amount of chloroform required. It is known that the actual bulk of an individual is the gross weight minus the stored fat; the presence of this reserve material in anæsthetisation actually subtracts and renders useless some of the chloroform which is administered.

What may be the actual chemical and physical effect of anæsthetics on protoplasm generally is a difficult problem, and one method which may be applied to its solution depends upon a study of the differences of potential which may follow the subjection of living nerves to anæsthetic vapour of known strength. N. H. Alcock[1] has extended the work of Waller,[2] and, in particular, has investigated the effect of chloroform and ether upon the current of injury which occurs in excised living nerves. A difference of potential existing between the longitudinal and transverse section of the nerve slowly declines under normal conditions, but the difference suddenly drops temporarily or permanently according as the vapour is weak or strong (12 per cent. or more). By subjecting certain regions of a nerve to chloroform vapour, it was noticed that an increase of the injury current, roughly proportional to the strength of the anæsthetic, occurred only when the vapour reached the cross section; applied to the longitudinal surface it caused a decrease.

The resistance of nerve is not affected by chloroform, and therefore no formation of ions at the expense of the electrolytes in the nerve takes place, but the normal polarisation of the nerve is markedly diminished.

A very significant fact is noted with regard to the conductivity of nerve before and after chloroform and ether. While the polarisation of the nerve was markedly altered (as Waller had found) there was no change in the electrical conductivity proper. If this is substantiated it would show that no fresh ion formation took place, and that no splitting up of ion-proteid occurred. In a second paper,[3] Alcock showed that while there might or might not be a combination of chloroform with the proteid of the frog's skin, the electrical effects could only be accounted for by supposing the existence in the tissues of either membranes

[1] *Proc. Royal Soc.* vol. lxxi. p. 264, vol. lxxiii. p. 166, vol. lxxvii. p. 267.
[2] *Proc. Physiological Soc.* November 13, 1897.
[3] *Proc. Royal Soc.*, B., vol. lxxviii. p. 259.

or surfaces of separation, so arranged that normally certain ions could traverse the membranes and others could not, while after chloroform these membranes or surfaces were destroyed. A simple combination of proteids, as in Moore and Roaf's theory, or with lipoids, according to Meyer and Overton, with chloroform would therefore be insufficient to account for the phenomenon of anæsthesia.

The Anæsthetic and Lethal Quantities of Chloroform in the Blood.

In 1860 Lallemand, Perrin, and Duroy stated that 100 grammes of blood contained 1 cc. of chloroform vapour. This was the lethal amount. In 1883, from the results of seven experiments, Gréhant and Quinquaud concluded that 50 milligrammes of chloroform in 100 grammes of blood was the anæsthetic quantity, which was only slightly less than the amount present at the lethal stage. It will be seen subsequently how very exact were both these determinations. Pohl's work in 1890 introduced a new method for the determination of chloroform in blood, and his chief conclusions were that the quantities of chloroform in the arterial blood of dogs during anæsthesia might vary. In some cases 100 grammes of blood contained ·05 gramme, in others only ·029 or ·018 of chloroform. The average lethal amount was ·035 gramme. Pohl also recognised that the lethal and anæsthetic amounts closely approximate one to the other. For about sixteen years no further researches were undertaken in connection with this question, but it was from time to time made abundantly evident that an accurate determination of the chloroform-content of blood was one of difficulty, owing to the tenacity with which the drug was held by the blood, so that it could only in part be recovered from that liquid or from the tissues of the body. During 1906 several French observers, and Buckmaster and Gardner in this country, have renewed this inquiry, and though the methods which have been employed in France and England are quite dissimilar, there is a fair uniformity in the results. The determinations of chloroform in the blood, made by M. Nicloux, St. Martin, J. Mansion, and Tissot, depend upon the titration of the chloroform as chlorides, which are obtained from the blood by distillation with alcohol, rendered

acid with tartaric acid, and subsequent saponification with alcoholic soda or potash. The end point of the reaction is a colour one, yellow potassium chromate changing to an orange-red silver chromate. Buckmaster and Gardner have criticised this method, not adversely or unfairly; but it was incumbent to do this, since Nicloux in particular, who has performed much work by this method, regards it as a very exact chemical procedure, and he also believes that results obtained by methods other than this one are too high.

The principal results obtained by the French observers J. Tissot,[1] Mansion,[2] and Maurice Nicloux[3] are described at length in a recent paper.[4] The last observer found that the anæsthetic amount varied for different individual dogs. The same is true for the lethal amount, and the differences between the amount required to produce an anæsthesia in which all reflexes are abolished and the lethal quantity are small. He also found that the quantity of chloroform present in the blood at the anæsthetic stage was almost constant, and independent of the weight of the animal—a conclusion really equivalent to the view that the quantity of blood in the individual does not modify the percentage of chloroform in the blood. Tissot's observations were also carried out on dogs, and the method for determining the amount of chloroform in the blood resembled that employed by Nicloux. The results of Tissot's work showed that anæsthesia can exist with a very low chloroform-content in the blood, and that the amounts in arterial and venous blood differ. During the administration of chloroform the amount in arterial exceeds that in venous blood; during recovery from narcosis more of the drug will be present in venous than in arterial blood. Tissot lays special stress on the point that when mortal syncope or failure of the heart-beat is produced in dogs with a prolonged administration of low percentages of chloroform, comparatively large amounts of the drug are found in arterial blood; but just before actual syncope occurs the amount falls in a marked degree. From this fact he concludes that this diminution in the blood, which is a constant phenomenon, is

[1] *Comptes rendus de la Soc. de Biol.*, 1906, pp. 195, 198, 200, 203.

[2] *Ibid.* No. 4, 1906, pp. 206, 238, 241.

[3] *Ibid.* No. 2, No. 3, No. 7, 1906, and November 2, 1907, p. 391.

[4] "The anæsthetic and lethal quantity of chloroform in the blood of animals," by G. A. Buckmaster and J. A. Gardner, *Proc. Royal Soc.*, vol. lxxviii. 1906.

accounted for by an excessive exit of chloroform from the blood into the tissues of the body, and especially the brain. On this fact Tissot lays particular stress. It is clear, assuming that the experimental data are beyond question, that the cause of death must be ascribed not to a gradual process by which a slow, progressive toxic stage is reached, but to a somewhat sudden change, due to a rush of chloroform from the blood into the body cells; and if this occurs, it will become necessary for us to modify our entire views as to the whole process of anæsthetisation: for other experimental evidence, some of which has been already given, indicates that, with a definite pressure of chloroform in the blood, a definite constant effect is exerted upon the cells of the body. These cannot and do not take up indefinite quantities of chloroform; they take it up in response to a definite solution pressure which exists in the circulating liquids of the body. This remarkable drop in the chloroform-content of the blood we have not observed, though, in view of Tissot's work, the possibility that it might occur was especially considered.

The method pursued by Buckmaster and Gardner in their experiments was as follows: In all cases the percentage of chloroform vapour in the inspired air was determined for each separate experiment. The amount of chloroform in the blood was estimated by the difference in chlorine-content of the blood before the administration of chloroform, and again at any subsequent period from the time when the chloroform-and-air mixture was inhaled. The destiny of inhaled chloroform is traced by its chlorine, and the blood during anæsthesia contains an excess of this element. Numerous control experiments were made in order to ascertain whether the percentage of chlorine normally present in the blood of an animal remains sufficiently constant during a prolonged experiment. This was found to be the case when ether was the anæsthetic used. Small amounts of blood withdrawn from time to time during such an experiment were also found to in no way affect the percentage of normal chlorine in blood. The chlorine was estimated by the method of Carius, which is the one generally used for the determination of iodine, chlorine, or bromine in organic compounds. A known weight of blood, about three to five grammes, is treated with nitric acid, and an excess of solid silver nitrate in a bomb tube heated to 200° C. for six hours. The amount of resulting silver chloride was then determined, and the difference

between the chlorine-content of the blood before and after anæsthetisation with chloroform was calculated, and this gave a figure which could be expressed as chloroform. The whole method is an entirely new one, and has never been employed by earlier observers. In exactness it is believed to be preferable to those methods where the determination is a volumetric one with an end point which depends upon a colour reaction. Most of these experiments have been carried out on cats, while other observers have generally carried out their investigations on dogs. The chief conclusions arrived at were that the amount of chloroform in arterial blood at the moment when some definite reflex action disappears varies with different individuals. The same is true for the lethal amount in the blood; but a consideration of all the experiments taken together shows that only a narrow margin exists between the weight of chloroform in the blood at the moment of anæsthesia (loss of conjunctival reflexes) and the cessation of respiration (lethal amount).

The above outlines the methods of investigation, and enables the conclusions to be represented in the following table:

Observer.	Animal.	Anæsthetic amount of $CHCl_3$.	Lethal amount of $CHCl_3$.
Gréhant and Quinquaud, 1883.	dogs	50 mg.	...
Pohl, 1890.	„	18–50 mg.	35 mg.
Nicloux, 1906	„	50 „	41–70 mg.
Tissot, 1906	„	34–40 „	60–105 „
J. Mansion and J. Tissot, 1906.	„	29 „	...
		32–43 „	...
Buckmaster and Gardner, 1906.	„	16–31 „ reflexes just gone.	61–69 mg.
Buckmaster and Gardner, 1906.	cats	14–27·5 mg. reflexes just gone	40 „

From these figures, which are in fair agreement, especially for the lethal dose, it would seem that the quantity of chloroform required to produce various stages of anæsthesia are somewhat higher in dogs than in cats. The difference, however, is not great. The lethal point is fixed as that at which the respiration is of a convulsive type owing to the onset of asphyxia.

The Rate of Assumption of Chloroform by the Blood

It is a familiar fact that when chloroform is inhaled the respirations may rapidly diminish in depth and frequency, or even actually stop within a few minutes. In the case of cats

it is exceedingly rare not to see this effect on a respiratory tracing. Any individual animal may exhibit this phenomenon in different degrees, and cessation of respiration may be permanent unless resort is had to some means of artificial respiration. Still more interesting is the fact that when the same animal is anæsthetised several times with the same percentage of chloroform vapour, this condition, which may be considered to indicate the first danger point in chloroform anæsthesia, occurs at the same time, and presents a constant type of impaired respiration. During this early period, in about two to three minutes after the administration of chloroform has commenced, a veritable danger point exists, and an elementary account of the physiology of this will be briefly described.

Nicloux points out that during this pre-anæsthetic period the intake of chloroform is rapid even with a low percentage of chloroform in the inspired air. Thus, within three minutes, 56 mgrs. per cent., an amount not much below the lethal quantity, were found in arterial blood when a somewhat large amount of the anæsthetic was supplied. Mansion and Tissot found that when a 4 per cent. chloroform-air mixture is inhaled, arterial blood becomes slowly but steadily charged with chloroform until the content of the drug in the blood is almost identical with the amount of vapour which it can hold *in vitro*. This is about 45 mgr. per 100 grammes of blood for an atmosphere containing 4 per cent. of chloroform (Tissot). After administration of this strength of chloroform, arterial blood contained the following amounts:

After . .	1 hr. 42 m.	1 hr. 50 m.	5 hrs. 15 m.	6 hrs. 56 m.	8 hrs. 21 m.
Mgrs. $CHCl_3$	27	30·5	36·7	42·4	46·2

In the experiments of Brodie and Widdows[1] the rate of absorption of chloroform during the introduction of anæsthesia was ascertained by allowing animals to inhale a known percentage strength of chloroform vapour, 1·06–2·78 per cent. Both the volume of air expired during any interval of time and the percentage of chloroform in this were determined, the latter by the same method which Vernon Harcourt had adopted, which depended upon the combustion of chloroform

[1] *Brit. Med. Journal*, July 14, 1906.

to hydrochloric acid. The chief new facts elicited by this work show, as might have been anticipated, that the rate at which chloroform is absorbed varies directly with the extent to which the lungs are ventilated. The slow and shallow respirations which occur so early in chloroform anæsthesia also stand in relation with a maximal retention of chloroform in the body, but how much of this is actually in the blood could not be stated. It is, however, abundantly clear that the minimum amount of chloroform in the expired air is found during the second minute, and from that period onwards the amount escaping from the body slowly rises. In a series of experiments, each lasting ten minutes, it was also observed that the amount of chloroform absorbed increased with the concentration of the drug in the inspired air, but the amount was not in proportion to the concentration.

In the experiments of Buckmaster and Gardner,[1] which were carried out on cats, small quantities of blood were withdrawn from time to time from an artery during the induction of anæsthesia with known percentages of chloroform vapour and air. The determination of the quantity of chloroform in these samples, ten or twelve in each experiment, afforded the data from which curves could be constructed. In all of the curves the same general features were seen. In the pre-anæsthetic period, or initial stages of anæsthesia, at a time when the individual is conscious, the chloroform-content of the blood rises with great rapidity to a value which approaches a maximum. During this period, which occupies the first few minutes, the first danger point in anæsthesia occurs, because the quantity of chloroform in the blood directly or indirectly affects the respiratory nerve-centres of the brain. In consequence of the respirations being slower and shallower, the amount of chloroform in the blood falls, but the fall is also due to the exit of the drug from the blood into the tissue-cells of the body. When the animal has passed this first stage the amount of chloroform again quickly rises towards a maximum value, and an equilibrium between the factors which determine the amount of chloroform in the blood appears to be obtained, the processes of intake and output of the anæsthetic at the surface of the lung going on side by side. In other words, a state of equilibrium is reached, which persists for a considerable period, and throughout this period the difference

[1] *Proc. Royal Soc.*, B, vol. lxxix. 1907.

between the amount of chloroform present in the blood and what is found at the lethal point is very minute. The state is far from one of safety, and the animal may suddenly die at any moment should any disturbing factors come into play. The whole of this period is a danger period. In the experiments quoted the percentage of inspired chloroform was maintained constant, but it is evident that the contention of those anæsthetists who have insisted that after anæsthesia has been established this can be and should be maintained with a much smaller amount of chloroform vapour, rests upon a sound basis.

Space does not allow of more than a reference to the heart failure which may occur in chloroform narcosis. An inhibition of this organ to such an extent that no blood can be driven through its chambers, though the heart is still beating, may occur at the first danger point of anæsthesia. Particularly valuable work in connection with this has been carried out by Embley,[1] Leonard Hill,[2] and by Brodie and Russell.[3] Studied from the point of view of a reflex action, the last observers have shown that a very close relationship exists between the respiratory tract and those nerve-centres of the brain which control the heart-beat, the respiratory movements, and the bore of the small arteries in the body. The most sensitive surface which, when stimulated, reflexly affect these centres is that of the lining of the nose, next the mucous lining of the larynx, and then the surface of the lungs, which are powerfully stimulated by vapours of chloroform, formaldehyde, and bromine. When the internal surfaces of the trachea and bronchi are irritated no reflex of the type just described can be evoked. Stopping of the heart alone is very easily brought about as a reflex action by stimulating the pulmonary branches of the vagus. The experiments of Embley have shown that for dogs the first danger point, cardiac inhibition, and consequent slowing of the respirations, can be entirely set aside by removal of the heart from the influence of the centres in the brain by cutting the two vagi nerves along which the impulses which check or arrest the heart normally pass. The effect of atropin, which cuts out the inhibitory influence of the vagus upon the heart, has been re-investigated by Schäfer

[1] *British Medical Journal*, April 5, 12, and 19, 1902.
[2] *Ibid.*, April 17, 1897, and December 1900.
[3] *Journal of Physiology*, xxvi. 1900.

and Scharlieb,[1] who have suggested its employment prior to chloroform anæsthesia. Embley and F. J. Martin[2] have also demonstrated the toxic effect of chloroform upon the unstriped muscle in the walls of the blood-vessels. These dilate when perfused with blood charged with a small percentage of the drug.

The Function of the Red Corpuscles in Chloroform Anæsthesia

Schmiedeberg was of opinion that the red corpuscles were the chief vehicles in the transport of chloroform from the lungs. This was supported by Pohl's experiments, and Nicloux, who used centrifugalised oxalated blood removed from a vein, recovered 64·4 per cent. of the chloroform in blood from the red corpuscles and 13·3 per cent. from the plasma. His figures for the distribution of chloroform among the constituents of the blood are much below those of Pohl, who had stated that 87-90 per cent. of the total chloroform was held by the red corpuscles; in other words, the chloroform-holding power of the corpuscles is seven to eight times that of the plasma.

Experiments undertaken by Buckmaster and Gardner, in order to ascertain how the anæsthetic distributes itself in the blood between the corpuscles and plasma, proved to be exceptionally difficult.[3] The separation of the corpuscles was accomplished by centrifugalising tubes of blood surrounded with ice, so as to hinder any clotting. Their conclusions, that chloroform is very firmly held by the blood of an anæsthetised animal, are in accord with all other observers. But it was also found that chloroform primarily associates itself with the red corpuscles and does not enter the plasma to any marked extent unless the anæsthesia is pushed to an extreme degree, or a chloroform-and-air mixture is administered with a high percentage of the drug. At the period when the reflexes disappeared the percentage of chloroform in the red corpuscles was found to be 64·3 per cent.; in another case 71·1 per cent., and after the inhalation of 2 per cent. chloroform for three quarters of an hour no less than 98·5 per cent. of the anæsthetic was held by the red corpuscles.

[1] *Trans. Roy. Soc. of Edinburgh*, vol. xli. Part II. (No. 12).
[2] *Journal of Physiology*, xxxiii. 1905.
[3] *Proc. Royal Soc.*, B., vol. lxxix. 1907, p. 566.

In order to obtain additional proof that the red corpuscles, as would seem to be the case from the above experiments, are the essential vehicles for the carriage of chloroform, Buckmaster and Gardner argued that if the view was correct that the transport of chloroform was a function of the red corpuscles, then, though the absolute amount of chloroform present in the blood might be modified by abstracting or adding blood from or to an animal, the *percentage of chloroform* ought to remain constant.

The general plan of the experiments was to anæsthetise an animal with ether or nitrous oxide, allow the anæsthetic to be disengaged from the body, and then administer a known percentage of chloroform. The determination of the amount of the drug in the blood was made at the asphyxial point. In one hour or an hour and a half all the anæsthetic was eliminated, and during this period a measured amount of blood was abstracted and the experiment repeated. In other experiments the amount of chloroform present was determined in the same animal before hæmorrhage, after hæmorrhage, and after the replacement of the blood which was furnished from another animal in such quantity as to augment the original volume of the blood by one-third to one-half.

The general results of all the experiments will now be detailed.

	Average amount of $CHCl_3$ per 100 grammes of blood. Before bleeding.	After bleeding.
Experiments in which the asphyxial state was rapidly reached, in about 3 to 9 min.	0·043 mg.	0·045 mg.
Experiments in which the asphyxial state occurred in about 30 to 80 min.	0·048 „	0·051 „

	After hæmorrhage.	After replacement of the blood.
Experiments made at the asphyxial point.	0·0421 mg.	0·0426 mg.
	0·0768 „	0·0768 „

	Before hæmorrhage.	After hæmorrhage.	After replacement of blood.
Experiments made at the asphyxial point.	0·061 mg.	0·059 mg.	0·049 mg.

From the above it would appear that the conclusion is justified that the percentage of chloroform in the blood does not undergo any variation corresponding to differences in the

volume of the circulating blood, and this is what was to have been expected if the red corpuscles were the essential agents for the transport of chloroform. It may be considered in the highest degree probable that the anæsthetic is associated with the proteins of the corpuscle, but the experiments naturally give no clue as to whether it is the hæmoglobin or other cell-proteins which actually pick up the drug. The earlier work of Hedin, Overton, G. W. Stewart, and Oker Blom, among others, on the permeability of the red corpuscles is of considerable importance in connection with the association of chloroform by the corpuscles. Stewart has pointed out that as far as certain electrolytes are concerned the permeability of the envelope alone, or of the whole disc, is dependent not on the life but on the structure of the corpuscles, for these, under a variety of conditions which are incompatible with life, and when the hæmoglobin is converted into methæmoglobin, preserve their permeability to some substances, but remain relatively impermeable to the electrolytes of the plasma. Hedin's experiments have demonstrated that some substances, such as sugar or sodium chloride, are unable to penetrate the corpuscles, while substances like urea, antipyrin, and the narcotic urethane easily enter them. The group of aldehydes, ketones, and alcohols, many of which affect the organism like the better known anæsthetics, if added to blood are found to be so distributed that nearly all the added substance is found in the red corpuscles. The significance of such experiments is great, for it establishes the fact that alcohol, or a narcotic, like urethane, can, and actually does, enter the cells of the body.

The Rate at which Chloroform is eliminated from the Blood after Anæsthesia

All observers are agreed that after the supply of chloroform is stopped the anæsthetic rapidly leaves the body. Five minutes after anæsthesia half the amount in the blood had disappeared; 7 milligrammes were found three hours later, and by the seventh hour the blood became free from chloroform (Nicloux). Tissot suggests that a study of the amount of chloroform in arterial blood should be made during the induction of anæsthesia, but that determinations of the chloroform-content of venous blood are necessary if we are rightly

to understand the rate at which it is eliminated. According to his experiments, the amount of the drug in venous blood constantly exceeds that in arterial during recovery from chloroform narcosis. Expressed in other words, directly the administration of the anæsthetic ceases the cells of the body begin to discharge their associated chloroform, and with this their functions gradually become restored. The subjoined table from one of Tissot's papers is of interest:

	Milligrammes of $CHCl_3$ per 100 grammes of blood.		
	Chloroform administration stopped.	45 min. later	2 hr. later.
Arterial blood . . .	53·2	5·8	0
Venous blood . . .	48·1	7·7	4·9

In our own experiments,[1] immediately the inhalation of chloroform stopped, a sample of blood was taken from an artery, and this was repeated at intervals, until half or three-quarters of an hour had elapsed. In other experiments venous blood taken close to the right ventricle of the heart was examined in the same way, while in a few experiments samples of arterial and venous blood were taken simultaneously. The main conclusion which can be drawn from these experiments is that the rate of elimination of the drug from the body *viâ* the blood depends upon the physiological state of the individual animal. The rate of loss is at first comparatively rapid, and subsequently becomes slower. But the initial rates of elimination are much less rapid than the initial rates of the intake of chloroform, and, on the whole, elimination is a much slower process than assumption, a view which is supported not only by the actual determinations of chloroform in the blood but by a comparison of the times at which the various reflexes disappear and reappear. From our curves the initial falls are not quite so rapid as the work of other observers had led us to suppose. The chloroform-content of the blood was only reduced by 50 per cent. in 15 to 20 minutes; three-quarters of the chloroform was eliminated in about half an hour. These statements hold good when the animal is breathing naturally, but, as might have been expected, the extent to which the lung is being ventilated during any period is the chief, if not the only, factor which determines the rate of elimination. Our experiments are in

[1] Buckmaster and Gardner, *Proc. Roy. Soc.*, B., vol. lxxix. 1907.

agreement with Tissot's observations, that at the moment when chloroform inhalation stops arterial blood contains an excess of the drug when compared with venous blood, but the difference between the amount of chloroform in arterial and venous blood after regular respiration is established is practically the same.

A sufficient and satisfactory explanation of the anæsthetic process probably cannot be given at present, but some conception of the anæsthetic state produced by the inhalation of chloroform vapour at about 2 per cent. may be attempted. It is true that data for this have been obtained by experiments on cats, but it is allowed that the phenomena shown by this animal during anæsthetisation closely resemble what is seen in man. The blood at first rapidly becomes charged with chloroform, which is held almost entirely by a protein or proteins of the red corpuscles. The respiratory centre or centres are at first stimulated, but these become affected quite early, and then discharge pulses less frequently and less efficiently than in a normal animal. In the dog especially, and to a less extent apparently in the cat, this behaviour of the centre is secondary to a weakening, or almost a cessation, of the activity of the heart. From this inhibitory effect the heart escapes, somewhat easily in the cat compared with the dog. The condition just described occurs early, within the second to the fifth minute, and may be considered as the first danger point in anæsthesia. In consequence of the slow and shallow respirations, the percentage of chloroform in the blood falls, either owing to a diminished intake of vapour or to the cells of the body storing up the drug at the expense of the blood, or because the elimination of the drug is as rapid, or more rapid, than the assumption. But the last cannot be the explanation, for the rate of elimination is by no means so rapid as is the assumption. The fall is, therefore, due largely to the disappearance of chloroform into the cells of the body, which, in virtue of their proteins, are capable of forming loose chemical combinations or aggregations with the drug. The cells are, in consequence, poisoned in varying degree. When the first danger point is safely passed, the respiratory movements improve in frequency and vigour, and this may be considered to represent a continuation of the initial stimulating effect of the drug, which was masked by the occurrence of a danger point. Thereafter the chloroform-

content of the blood quickly approximates to a maximal value, which is maintained until asphyxial convulsions occur. This may be termed the second danger period. The difference between the chloroform-content of the blood at the initial period, when the first danger point is reached, and also at the maximal value, when compared with the lethal amount, is very minute. The quantity of the drug in the blood governs the distribution of the anæsthetic which at first stimulates, and then finally paralyses certain cell districts of the body in definite order. Chloroform, therefore, though a toxic substance, does not produce its effects upon the organism by a cumulative action; these are not dependent upon the absolute quantity which is supplied, but upon the percentage-value of the drug in the blood stream.

THE REFORM OF THE MEDICAL CURRICULUM (II)

By PROFESSOR HENRY E. ARMSTRONG

Another act in the drama of medical education was recently played to a finish when the Senate of the University of London, at its November meeting, decided that it was unable to evolve a constructive scheme which would render possible the use of the great gift offered for the establishment of a school of preliminary medical studies at South Kensington. Like the truth, jealousy has prevailed: London seems to be ever at the mercy of contending factions—a natural result, perhaps, as she altogether lacks leadership.

I am constrained therefore to continue the article on the reform of the medical curriculum which I contributed a little more than a year ago to this journal and which, meanwhile, has met with a rejoinder from Dr. Wade (No. 4, April 1907).

Dr. Wade and I are obviously looking at things from different points of view: his being that we are living under almost ideal conditions, which cannot well be changed and which need not be changed; mine that we are in a time of makeshift: that it is our duty to take stock of the situation, to mend our ways without delay. Thinking that all is for the best in the best of possible worlds, he would pursue a *laissez-faire* policy. My desire is to see a new point of view introduced into the subject: it seems to me that it is useless to attempt to teach chemistry to medical students except as the study of function—the study of processes. Unless they can more or less understand the nature of the chemical processes which occur normally and under pathological conditions, as well as in some measure appreciate the alterations likely to be effected by changes in the conditions, they cannot possibly penetrate behind the veil which Nature at present draws in front of them.

I believe medical opinion will be with me; that many will agree with me that the preliminary studies, as at present conducted,

afford neither systematic scientific training nor proper technical training, the memory being merely loaded with a vast mass of uncorrelated facts, some of which, of course, are of interest and value: in the main, however, the time spent in acquiring them is ill spent, as a false direction is given to the mental activities. To give an example—happening recently to mention *Cholesterol* to a sharp young medical student now following the clinical course, I met with the pat reply—"Oh yes, that is the stuff in Lanolin: a monatomic alcohol, crystallising in rhombic plates with a bit snipped out of one corner, which gives a fluorescent red coloration with strong sulphuric acid." "Knowing that," said I, in amusement, "you must feel that there is nothing more to be learnt on the subject and that you are provided for life with information of inestimable value." "With information," said he, "sufficient probably to make the difference between passing or failing in the Second M.B." (at Cambridge). This illustrates, not inaptly, the present-day attitude, the kind of knowledge which it is thought is essential —and which is taught as essential.

It is worth while to examine Dr. Wade's case somewhat in detail. In discussing my qualifications to act as critic, he implies that I have taken an interest only in elementary school affairs and pictures me as a sort of educational Rip van Winkle, returned to the scene of my early labours with rusted barrel and decayed stock, unable to divest myself of old memories—thinking only of medical education as it was in the days when I took some direct part in it: the days of blackboard demonstration without practical illustration. I can scarcely think of myself as so entirely decadent. Like that contraption the Tar Baby, I may have worn the appearance of a mere scarecrow in medical eyes. Brer Wade forgets, however, that it is possible to lie low with eyes open; like Brer Rabbit, to take notice of all kinds o' persons, keeping the old woman at hand watching the kettle on the fire, in readiness when the time comes to pour down the "bilin" water on Brer Wade and his friends, practice having been gained meanwhile by spilling some of it on schoolmasters' heads.

Feeling as I always have and still do that a solid foundation is the first requisite, I have done my best to promote the introduction into schools of teaching calculated to develop some understanding of scientific method. Some little progress has

been made and in the last years of the old University of London, partly perhaps owing to my representations, some pressure was being brought to bear on the schools to make such teaching rational and effective. One of the first acts of the newly constituted University—one of its most retrograde and unforgivable acts—was to undo the good work of its predecessor. The protests made by those of us who had experience of the value of the system under which some knowledge of science was required of all at Matriculation were unheeded; we were advisedly excluded from all Committees dealing with such matters, and freedom to neglect their duty was conferred upon the schools preparing candidates for matriculation. Freedom, we all admit, is good in the abstract—but freedom is easily abused by those who are not ripe to enjoy it: for the most part, the schools were incapable of running alone—they were and still are in need of guidance.

Men like Dr. Wade apparently do not realise the truth of the adage that there are more ways of killing a pig than sticking it—that it is policy sometimes in hunting to approach your quarry in indirect ways—that there may easily be more haste and less speed—that it is well sometimes to play a waiting game, to exercise purpose silently. His present experience as a teacher of medical students is not very much greater than mine was when I gave up such work; since then I have been steadily engaged, I regret to say during five-and-twenty years, in educational research work—constantly making experiments, constantly thinking over and discussing the problems of education. My wits have been sharpened the more in that I have enjoyed an opportunity which has fallen, I think, to no other teacher of chemistry quite in the same degree—that of developing courses for and ministering to the wants of large special classes of students not destined to follow a chemical career, engineers mostly, first at the Finsbury Technical College, then at the Central Technical College. This more than anything else has led me to appreciate the possibility of teaching a subject in relation to its technical uses. I venture therefore to suggest that Rip has been active in retirement, not asleep; that he is down from the mountains by no means unfit for the fray.

And in other ways the course events have taken has been such as to impress me with a sense of the gravity of the

situation. But a few months after I commenced to breathe an atmosphere of apomorphine[1] at St. Bartholomew's Hospital Medical School in 1870, my chief Matthiessen came to an untimely end. I discovered him, one afternoon, asleep for ever, in his armchair: my first experience of real life—in itself an event to make a young man think. Had he lived, Barts might well have been made the centre of research on alkaloids and their use in medicine, a centre of inspiration—as he was a man of indomitable energy, full of scientific enthusiasm, with an extraordinary faculty of choosing workers and making them work; he had too the gift of insight and was interested in things organic and inorganic; in fact, he was a complete chemist in feeling: one who could determine electrical conductivities without lapsing into ionomania and who would have set his face against unreal, pretentious talk on the subject. His work on narcotine with Carey Foster and Alder Wright practically laid the foundations of alkaloidal chemistry. Whenever a chance comes to us in this country, however, we seem to let it lapse: lack of scientific training and of the scientific spirit has led the medical profession to overlook the advantages accruing from systematic research work, and the development of a narrow humanitarian spirit among the public now threatens to put a complete stop to such work in medical schools, as the hospitals are held to exist solely for the cure of poor patients: the number of persons, poor and rich, is in no way thought of who die lingering deaths because of our neglect to carry on systematic inquiry in directions likely to be of benefit to medicine. The chance once in the hands of Barts, thoughtlessly sacrificed, will not soon occur again, I fear.

In my former article, I spoke of a just feeling among medical men "that the present course in chemistry is a totally unfit preparation for medical practice"—and added: "this is the feeling we have to meet and provide for." Dr. Wade notwithstanding, I still affirm this to be the case, and I have reason to think that the teaching of other preliminary subjects is more or less open to similar criticism.

He has represented me as having made "an attack" on the curriculum of the University of London—in reality, my remarks

[1] Apomorphine was then under investigation and was in the air in more senses than one.

were of general application, the condition of schools outside London being at least as unsatisfactory as that of those in London.

I have led the reader who is unacquainted with the subject to believe, it appears, that medical education has remained unaffected by the rapid march of science during the past fifty years—actually I drew attention to the many improvements effected even during my time.

My remarks, Dr. Wade considers, might lead readers to believe that our whole system is radically wrong—they were intended to have that effect.

That the issue will be fraught with disaster unless the curriculum is remodelled, I have no doubt: it is already, in fact. Men are dying on every side owing to our inability to apply chemical knowledge to the interpretation of disease. Such homicide, however unwilful, must none the less come to be regarded as unjustifiable, if a consequence of ignorance which it is in our power to overcome. And it is in our power to overcome it, at least partially.

A stern duty may also lie before medical men for which they will have to be prepared. Many are living whose existence perhaps is a matter of extreme danger to the State, as the perpetuation of their kind may be expected to have the most serious consequences. The problems of heredity need consideration from this point of view; unless medical men can undertake their study and act as advisers of the public, society will not receive that protection which sooner or later it will come to expect from the medical profession.

Although surgeons have advanced their practice by leaps and bounds, that of medical men has almost stood still: the great improvements—such as the treatment of rabies and diphtheria by appropriate antitoxins and the various new potent drugs, not forgetting lumbar anæsthetics—are due to chemists. The fact is the medical man is not sufficiently versed in scientific method to undertake the diagnosis of the obscure phenomena of chemical change in the complex material which constitutes the human body. He understands but few simple chemical changes occurring in test tubes—the complexities of change under vital conditions are entirely beyond his ken and grasp.

The case is well stated by Archdall Reid in the following passage (*The Principles of Heredity*, 2nd ed. 325):

The principal aim of that part of formal education which is not specially intended to supply the individual with useful knowledge should be to develop his reflective powers. Much scientific teaching as practised at present does not fulfil this condition. For example, the medical profession includes the largest number of scientific men in the world. From first to last during his career the medical student is loaded with a monstrous and ever-increasing burden of facts, but no systematic effort is made to increase the acuteness and range of his thinking processes. A great deal of the burden on his memory is necessary ; but not all of it. Thus since he treats the ailments of an animal, man, largely by means of vegetable drugs, he is taught botany and zoology. In botany he learns such things as the peculiarities which distinguish various natural orders of plants from other natural orders. In zoology he acquires a more or less elaborate knowledge of the structure of certain types of animals—the vascular system of the sea-urchin, the organs of generation of the earthworm, the skeleton of the frog, the bones of the cod's head, the dentition of the different species of mammals and so forth. But no man is a better physician for knowing the difference between a raceme and a rhizome, nor a better surgeon because he has studied the anatomy of the cockchafer. His subsequent experiences do not link up with these fragments of knowledge which, though necessary to the equipment of the professional botanist and naturalist, are so remote from the labours and interests of the medical career that presently they are forgotten. In the end the average doctor has a knowledge of botany and zoology not much more profound nor useful intellectually than that possessed by the average farmer or stockbreeder. Either he should be otherwise employed during his earlier studies or his later work should be so modified as to link up with them. Facts, scientific or other, have by themselves no intellectual or scientific value. It is the recognition of the relationship between facts in a natural group and between different groups that confers the value. No doubt medical students, in proportion to their intelligence, get a general notion of the essential likenesses, which, amid distinguishing differences, bind together all living nature. But this result, if it be the one sought, is attainable by direct teaching at a hundredth part of the cost in time and labour.

It is the misfortune of the public as well as of the medical man that he is placed in this position. And to him before all others it is of importance to remove the disability from which his profession undoubtedly suffers. He can help more than most if he care to act—as there can be little doubt that the public would be advised by him. The clergy no longer count in education—as a body they have ceased to take an interest in the subject, and their interests are thought to be so opposed to those of the modern scientific school that they are not likely to intervene on behalf of training the value of which they are entirely unable to appreciate. It is the more important, therefore, that medical men should recover the position they formerly held in common with the clergy, as men of culture.

In defending myself against the charge of being asleep—as Dr. Wade suggests that my allegations are vitiated by inability

to divest myself of old memories—I may not unfairly point out, perhaps, that my critic is not yet awake to possibilities which I seem to see clearly. His conservative attitude is in itself proof that he is scarcely qualified to enter on a discussion such as we are now engaged in. His connection with the subject of medical training arises rather from his being in a medical school than of it. Apart from his obvious lack of feeling on the physiological side, in common with so many other chemists he in no way realises apparently how vast is the change which has come over chemistry within recent years, making it possible to teach the subject far more effectively than formerly. Herein lies the difficulty. Our brains are addled by the constantly increasing load with which we weight ourselves. Very few can see their way out of the wood for the trees. We do not even know how to use books effectively and insist on our students learning off everything by heart instead of teaching them to understand principles and economise effort by referring to their books for detailed information when occasion arises.

Dr. Wade argues that the teaching is enormously improved. Formerly, he says, the scientific spirit was absolutely destroyed by blackboard demonstrations without experimental illustrations and no opportunity was given to the student of verifying his teachers' statements: it is quite otherwise now. Is it? Does the average student gain much from seeing a few practical demonstrations in the course of a lecture or from preparing a few substances in the laboratory? I doubt it. The intelligent man in the old days learnt from lectures practically as much of things essential as the intelligent man does in these days: then as now far too much attention was paid to mere fact knowledge, to the kind of fact which comes into prominence, for example, in Dr. Wade's own book—of its kind, a very admirable one—or as illustrated above by the reference of my young student friend to cholesterol. The one real improvement in the course is the introduction of simple quantitative laboratory work, such as I pleaded for in my B.A. address in 1885—conceptions are established in the mind of the student by such work which are invaluable.

Instead of dealing with irrelevant matter, says Dr. Wade, the proximate constituents of the food, degradation products of the body, urea, etc., are considered. The same were dealt

with in my day. The question is—How are they dealt with—any more usefully than formerly? I doubt it. Murder will out, and out it comes when Dr. Wade tells us that "Chemistry for medical students bears precisely the same relation to physiology and pathology as anatomy does, the chemist dealing with the nature and relation of the materials and the anatomist with the nature and relation of the structures the function of which, in both cases, it is the part of the physiologist to investigate." Chemistry as thus defined by Dr. Wade is a kind of dry-bones business—and so it usually is; the chemistry the medical man needs, however, is not for the most part anatomical but functional: physiology, therefore, in a large measure, overlaps it. This is what Dr. Wade and his friends do not see—but they must come to recognise it, sooner or later.

Students, in his laboratory, says Dr. Wade, dissect chemically and, where possible, reconstruct artificially, compounds such as urea. Suppose they do—how much better off are they? As ordinarily conducted, the exercise is an almost worthless one, in my opinion. And from a medical point of view, it doesn't really matter what urea is: a harmless waste product, containing oxygen and nitrogen in their lamest form, its importance is generally much overestimated in chemical circles, just as we now have reason to suppose it was by Fick and Wislicenus, who spent much unnecessary effort on the Faulhorn in worship of its supposed functional significance. The student does not really dissect it when he gets ammonia, etc., from it any more than an anatomist dissects a bone when he gets calcium phosphate from it; probably, moreover, urea is not what he is commonly taught to suppose it is—*carbamide*. Long absorbing conversations which I had with Peter Griess—the prince of nitrogen chemists—in days of yore rise in my memory when I write this: he would not listen to its being called carbamide.

The really important problems centring around urea are not taught—the wonderful inter-relationship of the closely allied forms of the compound CON_2H_4; the condition of equilibrium in which urea, carbamide and ammonium cyanate subsist in solution: although probably of high physiological importance, these subjects are considered to be far too difficult for the medical student to tackle; really they are the points which he should be led to study very thoroughly. From the medical point of view, the substances which accompany urea

in urine in fluctuating proportions are far the more important —as they are often of diagnostic value.

If those to whom I am addressing myself scarcely grasp the force of this argument, they will nevertheless see, assuming my contention to be correct, that the suggestion that chemistry is taught in medical schools in an unsympathetic manner cannot be so far from the truth after all!

Dr. Wade altogether objects to the proposition that we might well give some consideration in the first instance to complex cases, such as the processes of digestion, for example. From the objection he makes, it is clear that he in no way appreciates the marvellous advance made in this field of late years. Knowing as we do now the fundamental importance of enzymic action both in up-grade and down-grade processes, it is clearly our duty to make this a primary subject of study. Colloid substances also invite special attention and such simple substances as water, which now is scarcely considered, although physiologically perhaps the most important constituent of the body; what is taught about it—its composition, etc.—is worthless for all practical purposes.

According to Dr. Wade, present-day examinations in science are very different from and better than those held when I taught medical students. They are absolutely the same, except—and the improvement is a real one—that simple quantitative exercises have been introduced into the practical chemistry examinations. When I contrast the questions set last year with those set twenty-five years ago, I find no difference: the same stock academic riddles are propounded year after year. At no time have the questions had any real bearing on the problems which face the medical man; those set during the past year or two are as futile as those which I assisted in setting in the early 'nineties, although meanwhile, as already pointed out, there has been a vast development of knowledge.

The main lines on which chemical change proceeds having been made clear to us, there is no question that it is now possible to teach a chemistry which should give eyes to the medical man and enable him gradually to pierce the gloom which still enshrouds the subtler changes: I therefore contend that we are much behind the times.

Dr. Wade not only says that chemistry is now taught (in

the London Medical Schools) with direct reference to its scientific application in physiology and medicine, but that the curriculum laid down for medical students has been specially constructed and, except in the purely elementary parts, is essentially different from that laid down for chemical students. Let us see if this be so. I take the following first year's course of study from the Regulations (issued in September 1907) in the Faculty of Medicine for Internal Students:

Inorganic Chemistry

The *Curriculum* in Chemistry shall consist of not less than sixty Lectures and one hundred and twenty hours' Practical Work in the course of an Academic Year. The Syllabus is as follows:

I.—For Lectures

Illustrations and examples of chemical action. Solution, crystallisation, distillation, sublimation, precipitation. Mixtures and single substances, separation and decomposition.

Gaseous and liquid diffusion.

Indestructibility of matter. Elements and compounds. Laws and condition of chemical action.

The atomic theory. The determination of molecular weights, equivalents and atomic weights. Valency and structural formulæ. Equations. Chemical calculations.

Classification of the elements, including the periodic system. Synthetical production of compounds from their elements. The general characters of the chief types of compounds. Acids, bases and salts. Chemical nomenclature and terminology.

The principles of gravimetric and volumetric analysis.

Production and properties of the more important and typical elements and of their most familiar compounds.

The character of chemical changes, including the study of simple exothermic and endothermic reactions, thermal dissociation, electrolysis, catalysis, mass-action and rates of reaction; the conditions which determine and influence such changes and the attendant phenomena. Osmotic pressure.

The above to be illustrated by a detailed consideration of the following:

Oxygen, Nitrogen, Hydrogen.—Chemical nature of the atmosphere; composition and properties of water; natural waters; the oxides of nitrogen; nitrites and nitrates; ammonia, ammonium salts, hydroxylamine; hydrogen peroxide, ozone.

Carbon.—Its oxides, carbonates; relation of carbon dioxide to animal and plant life; carbon disulphide; coal and coal-gas; combustion; nature of flame; cyanogen, hydrocyanic acid and the metallic cyanides.

Fluorine, Chlorine, Bromine, Iodine.—Their compounds with hydrogen; oxides of chlorine, hypochlorites, hypobromites, chlorates, iodates.

Sulphur and Phosphorus.—Their compounds with oxygen and hydrogen; chlorides of phosphorus; sulphides, sulphates, sulphites, sodium thiosulphate; phosphates.

Boron and Silicon.—Their oxides; boric acid and borax; silicon fluoride; nature of glass.

Occurrence in nature, sources and preparation of the following metals and their principal compounds, omitting metallurgical processes: lithium, sodium, potassium; calcium, strontium, barium, magnesium, zinc, cadmium; copper, silver, mercury; iron, aluminium, chromium; manganese; lead, tin; arsenic, antimony, bismuth.

(N.B.—The whole subject will be treated in an elementary manner.)

II.—For Practical Work

The Course must be such as will enable Students—

(*a*) To prepare and demonstrate the properties of common metallic and non-metallic substances and to purify them by precipitation, crystallisation or distillation.

(*b*) To perform accurately the following simple quantitative operations: the determination of the equivalents of copper by reduction of its oxide and of copper, tin and zinc by oxidation; alkalimetry and acidimetry; the estimation of chlorides gravimetrically and by titration with silver nitrate; and determinations involving simple applications of the permanganate and iodine thiosulphate processes.

(*c*) To identify by simple tests the common elements and their more familiar compounds, including mixtures which may contain not more than one acid and two metals belonging to different analytical groups.

(*d*) To write out a clear account of their practical work, accurately describing the nature of the processes employed and, where possible, representing by equations the chemical changes involved.

To my thinking, the course here laid down is an ordinary, thoroughly old-fashioned and conventional preliminary course of inorganic chemistry. There is not a single word to indicate any connection with either physiology or medicine. It scarcely differs from the 1890 scheme, except in the practical part, *a* and *b* in this being new: (*b*) is admirable in principle: the improvement in teaching, to which Dr. Wade refers, in my opinion is due to its introduction; what (*a*) may or may not mean it is difficult to say.

The current scheme for chemistry in the Faculty of Engineering is as follows:

The methods which lead to the discovery of the composition of common materials occurring in nature.

The determination of molecular weights, equivalents and of atomic weights. Valency and structural formulæ.

Classification of the elements, including the Periodic Scheme.

General characters of the chief types of compounds, including acids, bases and salts and a few prominent carbon compounds, especially as illustrating the relations of properties to composition and structure. No distinction will be admitted between Organic and Inorganic Chemistry.

History, production and properties of the more important and typical elements and their most familar compounds.

The character of chemical changes, including combustion, thermal dissociation

and electrolysis; the conditions which determine and influence them and the attendant phenomena.

The whole to be treated in an elementary manner.

Tersely worded as it is, this is infinitely superior to the medical scheme as a statement; but it is essentially the same scheme; not essentially different from the latter. The fusion of organic with inorganic chemistry, which Dr. Wade speaks of as having been tried with disastrous results, is treated, it will be noticed, as an accomplished fact.

Passing to the second year's course, we have the following :—

The *Curriculum* in Organic Chemistry shall consist of not less than sixty Lectures and sixty hours' Practical Work in the course of an Academic Year.

The Syllabus is as follows :

I. For Lectures

1. Purification of solids and liquids.

2. Analysis of organic compounds. Estimation of carbon, hydrogen, nitrogen, sulphur, phosphorus and the halogens.

3. Empirical and molecular formulæ. Determination of molecular weights.

Students will be expected to know the general properties of the following groups of compounds, illustrated in each case by reference to a few of its more important members :

Aliphatic Series

Paraffins (especially methane and ethane).

Unsaturated hydrocarbons (especially ethylene and acetylene).

The different classes of alcohols and their derivatives (with special reference to methyl alcohol, ethyl alcohol, glycerol and mannitol).

Aldehydes (with special reference to formaldehyde, acetaldehyde and chloral hydrate).

Ketones (with special reference to acetone).

Acids (with special reference to formic, acetic, lactic, oxalic, succinic, malic, tartaric and citric acids).

The preparation and properties of the following derivatives of acetic acid : acetyl chloride, acetic anhydride and acetamide.

Simple ethers (with special reference to ethyl ether).

Esters (with special reference to ethyl acetate and saponification).

Amines. Amido-acids. Glycocoll.

Carbohydrates. Sugars (and more especially glucose, fructose, lactose, maltose and cane-sugar). Starches. Glucosides.

Cyanides. Urea. Uric acid.

Aromatic Series.

Hydrocarbons : benzene, toluene and their simple derivatives.

Sulphonic acids.

Phenols (with special reference to phenol, catechol, hydroquinone and resorcinol).

Benzyl alcohol. Benzaldehyde.

Acids. Benzoic acid. Salicylic acid.

Pyridine.

(N.B.—The whole subject will be treated in an elementary manner.)

In 1890, the Organic Intermediate course was as follows :

The composition, the properties and reactions and the more important derivatives of the following substances :

The principal series of Hydrocarbons (with special reference to their chief Haloid and Nitro-derivatives).

The Ethylic series (with special reference to ethers, esters or ethereal salts, aldehydes, ketones and acids).

Glycol. Glycerine ; natural fats.

Amylaceous and Saccharine substances.

Vegetable acids.

Benzene and Toluene with the principal Phenols and Nitro-derivatives.

Ammonias and the more important natural Alkaloids.

Amides, Urea, Uric Acid.

Cyanogen, Cyanides, Cyanates and Cyanurates. Glucosides.

The processes of Saponification and Fermentation.

The principles involved in Ultimate Organic Analysis and in the determination of Molecular Weight.

Again, the difference is merely nominal, except in the practical work, which is now slightly superior to the old pass but inferior to the old honours examination, as this included the volumetric Pharmacopœia work. It is noticeable that hydrolysis and fermentation could be examined on in 1890 but that the latter is now left out, although of infinite importance from a medical point of view. Evidence that the subject should be taught with direct reference to its scientific application in physiology and medicine can only be found in the entire absence of reference to this desirability. Indeed, with such syllabuses in operation, the authorities have no right to expect any special knowledge of medical applications from candidates—and the examination papers show that the examiners are either alive to this fact or are unable to deal with the medical aspects of the subject.

In the true school of the future, teachers will not be restrained by stereotyped syllabuses ; they will teach what is necessary without reference to any narrowing schemes such as are now forced upon them by persons who have no proper understanding of the actual work. The syllabus is always a compromise and representative of mediocrity ; it never reaches the high-water mark of experience in a subject.

It will be noted that the time prescribed for laboratory work in both years is only twice that to be devoted to lectures. Whether the time be sufficient or not need not be considered ; it is certain, however, that long courses of lectures are now thoroughly discredited as a means of giving elementary instruction.

Turning now to the consideration of the future, the task before us is clearly that of rendering our Universities efficient as educational machines; at present, they are almost beneath contempt as such, owing to the lack of effective organisation—to the lack of true ideals and of active co-operation among their workers; so much is this the case that they may be said to exemplify human frailty rather than human faculty. Taking London as an example, the whole of the University organisation proper is practically worthless, except as a means of retarding progress: the only useful parts are the individual Schools; instead, however, of recognising the importance of these and facilitating, improving and harmonising their work, the University machinery is made use of mainly as a means of stultifying their efforts—the attempt being made persistently to reduce all to one dead level of uniformity.

Dr. Wade is one of those who at the last senatorial election took a prominent part in depreciating the efforts that are being made to develop systems of training suitable to the times by allowing himself to become an advocate of the policy of the Graduates Association. The professed object of this Association is to maintain a rigid, uniform system of examinations for so-called external and internal students alike; and its professed policy is one of antagonism to the teachers in the schools. Of course, the contention is that the agitation is on behalf of the maintenance of a pristine standard, which is painted as having been a very high one—but those who defend this position forget to inquire whether the standard may not have been merely one of difficulty rather than one of excellence; they at least quietly, if not advisedly, ignore this possibility. Those who are behind the scenes know full well that excellence is not thought of. The struggle is between two systems: the one being that of the Schools—in which the attempt is being made to develop practical methods of teaching, having practical ends in view; the other being that of the Coaches—whose object is to secure the immediate success of their pupils at the examinations. The issue will be determined by public decision in favour of one system or the other: the public must determine whether its interests are best served by a system which, if properly administered, cannot but afford training likely to promote efficiency; or by one which tends rather to the stultification of faculty, its end being the immediate, always more or less faulty

solution of a series of Chinese puzzles having no relation to the requirements of life, not competency and skill in doing actual work.

The University machine must be made sound in its working parts, if it is to run smoothly and effectively.

> "What's the good of Mercator's North Poles and Equators,
> Tropics, Zones and Meridian Lines?"
> So the Bellman would cry; and the crew would reply,
> "They are merely conventional signs!"

And so it is with the Senates, Faculties, Boards of Studies and all other such institutions—for the most part, they are mere time-wasting contrivances; the Schools are the one essential feature of the University organisation: if they are guided by true ideals and in honest hands, they may be counted on to do effective work—not otherwise: no mere ordinances can help them; suspicion of the teachers can only nullify their efforts.

To put the teaching of the preliminary medical subjects on a sound basis in London, the first thing to do is to establish a limited number of special Schools. Whatever the present feeling of the various Institutions may be, however jealous they may be of one another, this step will necessarily be taken at no distant date. The public will demand it, as the only means of securing efficient teaching. The development of a suitable course of preliminary studies must be a matter of experiment—it must therefore be in the hands of an independent body of competent teachers: of a School free from interference and independent of external control. If University privileges are to be attached to the Schools, they must be of a certain importance. I imagine that at most three such Schools are required and can be allowed in London. It is most unfortunate that a beginning was not made at South Kensington.

My own personal experience—far from being of the antediluvian order painted by Dr. Wade—enables me to speak with some slight feeling on a proposition such as I advance above. When Prof. Ayrton and I were appointed in 1879 by the City and Guilds of London Institute for the Advancement of Technical Education to start classes in temporary quarters at the Cowper Street Schools, Finsbury, I found plans already drawn for the erection of a separate chemical laboratory on an adjoining site. I at once urged that these should be set aside

and that a more comprehensive scheme should be developed, in order that students might receive the general training required to fit them for industrial posts. Plans were elaborated by us with the assistance of Mr. E. C. Robins, an architect and a member of the governing body; later on, in conjunction with Prof. Perry and Mr. Magnus (now Sir Philip Magnus), we drew up the scheme under which the Finsbury Technical College has been worked practically up to the present day. The passing of a simple examination was made a condition of entrance, from the beginning.

We made it a fundamental condition that there should be no external control through examinations, feeling as we did that it would be impossible to develop suitable courses of instruction if the College were hampered by the necessity of following instructions laid down without any reference to the particular work to be accomplished. The Finsbury College has been a remarkable success; the elimination of external examinations has in no way had the detrimental effect pictured by Dr. Wade (p. 639)—on the contrary. Unfortunately, all the Polytechnics which came into existence subsequently elected to worship at the examination shrine—in most cases their progress has been most seriously hampered by this circumstance. At the close of the Inaugural Lecture which Prof. Ayrton delivered at Finsbury, on November 1, 1879, after referring to the wonderful development of the Japanese during the previous ten years, he pointed out that what the City Companies proposed to do was to give workmen that education which will enable them to commence doing what George Stephenson, half a century ago, urged on them: "Learn for yourselves, think for yourselves, make yourselves masters of principles, persevere, be industrious and then there will be no fear for you."

The keynote of the work at Finsbury was struck in this passage.

When in 1885 we passed to what is now the Central Technical College, together with our colleagues we elaborated a scheme which was dominated by this same policy—again we were uncontrolled by external examinations. The success which has attended the College—the fact that it now ranks as the premier Engineering College in the country—is proof that such a system works well in practice. In point of fact, it would not have been possible, we believe, to achieve success under any

other less elastic system—the constant modification and improvement of the courses which time has shown to be possible and desirable could not otherwise have been effected. The purpose with which students work would have been altogether different: instead of concentrating their attention on their work and acting under the advice of their teachers, they would have constantly had in mind the possible requirements of the examiners and the nature of the Chinese puzzles they would be called upon to answer. Only those who have worked untrammelled by the cast-iron conditions of a rigid system of external examinations are aware of the terrible limitations which such a system imposes upon both teacher and taught.

In both schools, class examinations have always been held. Of late years, we have had the opportunity at Kensington of testing the effect of holding the examinations at the conclusion of the first year's course in conjunction with external examiners appointed by the University of London and of counting the examinations as the Intermediate examinations for the University degree. The examinations, however, have been strictly on the courses and the practical work done during the whole period of study has been taken into account, students being required to have done this as well as the written work satisfactorily. The effect has been altogether good—whereas formerly students would pay little attention to a subject which did not happen to appear in the University syllabus and were liable to neglect their work while preparing to solve examiners' riddles, they now realise that it pays to give serious attention both to lectures and to laboratory work.

The teaching staff at the Royal College of Science, the Royal School of Mines and the Central Technical College have considered the matter together and are unanimous in thinking that the method now applied to the Intermediate is the only proper method to be applied in future to the degree examination (the B.Sc.).

The report has been most sedulously propagated, for political purposes, by Dr. Wade's friends in Convocation that internal students pass the examinations without any effort, far more easily than the external. I know the very reverse to be the case. It is now possible to insist on a high standard of practical work; and it is possible also to penalise the abominable practice of "cooking" results, which seems to be regarded

with entire equanimity by most schoolboys. Under the present external system—although only a few fail to pass who are thoroughly well trained and deserve to succeed, through bad luck in meeting with unfamiliar questions or nervousness—many get through who have no right to pass, being merely crammed for the occasion.

The introduction of the internal system is, in my opinion, the one step of importance taken since the reconstitution of the University—and it was forced on the University by the Schools.

In the course of a speech which he delivered last year, as Chairman, at a dinner of the Graduates Association—which has been printed and widely circulated—the present Vice-Chancellor of the University said that the Association "agreed with Lord Derby in distrusting the teacher as the examiner for degree examinations and does not approve the adoption of degree examinations to fit the teaching of a particular college or Professor." Such a libellous aspersion of the teacher can only be met with the contempt it deserves—but the statement embodies popular doctrine and until teachers are held to be above such suspicion there can be little improvement of their position. The members of the Association who are teachers might well consider whether in thus casting doubt on the honesty of their class, the Chairman is rendering them a service—whether after all they are not catspaws in an agitation which has but commercial ends in view. The narrowness of liberal opinion is too well known to require elucidation and the general tendency to jump at conclusions is well known: but before giving vent to such utterance, the Vice-Chancellor might well have paused to consider whether he and his friends, Lord Derby included, have been in the possession of the knowledge necessary to the formation of a valid opinion. Dr. Wade has described the teaching of my early days as "absolutely destructive of the scientific spirit"—as I had the privilege of numbering the Vice-Chancellor among my pupils, it may be that I am in part responsible for his lack of scientific acumen. But I cannot help thinking that the experience he has had since coming into office and the more intimate knowledge he has gained of the University under somewhat modernised conditions—far removed though these

may be from what is desirable—will have convinced him that his dictum is now not of general application, even if he be not yet prepared to admit that it does not apply at all to true University teaching.

In the case of special schools such as I advocate, the teaching should be entirely under the control of the School, including the examinations on the course held in conjunction with qualified external examiners appointed by the University—whose part, however, should be that of sympathetic advisers rather than that of fault-finding critics. The condition of entry should also be determined by the School alone. It is to be hoped that, at no distant date, examinations such as the London Matriculation will come to an end, as being wholly bad in their influence on the schools from which candidates are drawn: owing to the failure of the University to lay down proper conditions and the lack of competent examiners, there is no real standard of excellence but only one of difficulty.

The matriculation examination may be considered to be of value from two points of view—either as affording proof that the person who passes has received a sound education at school; or as proof of fitness to enter on a course of University study. As at present conducted, it subserves neither purpose properly. It is well known that the requirements are not such as can be directly met by schools and that it is necessary to prepare candidates specially for the ordeal, a thoroughly demoralising proceeding. Moreover, those who have passed the examination, judging from my own experience, are in no way specially fitted to proceed to higher studies. During several years past I have each year had the opportunity of comparing the work done by a considerable number of students who have passed the London Matriculation with that done by at least an equal number who have not submitted themselves to this ordeal: although a distinct difference has been noticeable between the two classes—inasmuch as the former have been more assiduous workers, less anxious to waste their time, being drilled in learning lessons—the one class has not been in any way better prepared than the other to enter upon technical studies. The work done in preparation for the University examination has been in no way of special advantage to the students and has not had the effect of rendering them more intelligent: both classes have been

equally incapable of using their own language effectively in writing accounts of their work, equally untrained in the use of books, equally lacking in manipulative skill. Indeed, the non-matriculated students, on the whole, have had freer minds and from this point of view have been better students. The impression I have gained is that the matriculation is of value only as a proof of ability to pass an examination of a particular type—of the literary type; in fact, the chief tendency of the examination appears to be to bring about the selection of a bookish type of student. I am persuaded that for all practical purposes a properly conducted College entrance examination is both far superior to the matriculation and free from its unfairness—for many are denied access to the University degrees by failure at matriculation who are quite able to follow University courses of instruction with profit, improving vastly as they gain in experience. It is perfectly easy, in a college entrance examination, to judge which of the candidates are likely to be able to follow the courses; in the few uncertain cases, no doubt remains at the end of the first or second term of instruction and incapables are then easily weeded out.

But the whole subject is full of difficulty. At present we are but moving in a vicious circle. The work done in the schools is unsatisfactory as a preparation, in laying a suitable foundation, for the work to be done at the University; the Universities, however, exercise no proper influence on the schools, owing to the academic unpractical character of their entrance examinations. The two centres of activity need to be co-ordinated and to be brought into effective co-operation. The only way in which it appears probable that we may succeed in introducing the desired reforms is by linking up the secondary schools directly with the University schools, by leaving these latter to determine the conditions under which entry to their courses shall be accorded to scholars from secondary schools. But it will be desirable, as far as possible, to dispense with entrance examinations and to exact evidence of training instead. The system in vogue in the Universities of the Middle-West in the United States of America appears to be the one most deserving of trial. This involves the inspection of the secondary schools by *competent* persons from the University schools and the admission forthwith at the University

of pupils from schools duly accredited as providing satisfactory instruction. If during a series of years the pupils from a particular school prove to be unsatisfactory students, the school is struck off the list. A system of this kind would make it possible to bring about the necessary changes in our school system within a very few years—if they entered into the work in the right spirit, University teachers would be able to give advice and assistance to the teachers in the schools which would make it easy for them to improve their teaching. A new spirit of co-operation would be introduced which could not fail to have far-reaching consequences. No headquarters machinery will effect the object I have in view.

Dr. Wade has spoken of the time devoted to preliminary medical studies, especially chemistry—he says, the work cannot be done in less time than is devoted to it at present and more it is impossible to give. The question is one for the future to decide. In my opinion—and I speak from considerable experience—it is undesirable to keep boys and girls at school much beyond sixteen years of age, certainly not beyond seventeen; after this age, they lapse into unsystematic if not irregular habits and are subjected to a discipline unsuited to their years. All further education should be carried on at a place of higher education, under more elastic conditions than school affords and more in sight of the world; under conditions likely to develop independence of character and individuality. On the other hand, it is undesirable, as a rule, that a student should take up serious clinical work under hospital conditions before he is one- or two-and-twenty years of age—the strain is too severe for younger men and the necessary maturity of judgment is rarely developed at an earlier age. From sixteen or seventeen at latest to one- or two-and-twenty should be a period of sufficient length, under proper conditions, for the mastery of the various subjects comprised in the curriculum, short of the purely technical stage. More time could well be found for chemistry than is now given to the subject and as the medical man is, in large measure, a practising chemist, it will come to be recognised, I believe, that he must acquire a sound working knowledge of the subject. Let me add that I would make literary training an important element in the curriculum

As to the teachers—Dr. Wade contends that chemistry must be in the hands of chemists. I agree. But the chemists must be physiologists. The chemistry to be taught will not be mere dry-bones chemistry—anatomical chemistry—but functional chemistry, physiological chemistry in the true sense of the term. Few among our present race of chemists are physiologists even in their own domain; they are mostly mere anatomists. It will be necessary to educate a new type of teacher for the purposes of the medical schools—one who is in full sympathy with medical aims, able to appreciate the character of the problems with which he is faced—a physiological chemist, in fact; it will be necessary, on the other hand, to have physiology taught by chemical physiologists, men who have the same appreciation of chemistry that chemists will have of physiology. The one will have a mastery of the technique of chemistry, the other of the technique of physiology—both sympathising with each other's aims and objects more than either does at present.

As to the state of knowledge of students entering the medical schools, I am quite at one with Dr. Wade that for some time to come it will be necessary to deal with the scientific subjects almost *ab initio*. But I am not inclined to adopt his *laissez-faire* policy as the policy of the future. I hold that it is the duty of the Universities to take the schools in hand without delay and force a sound policy on them. Of what use are Universities if they cannot control the course of higher education—if they do not act as advisers of the public—if they do not promote the spread of new knowledge? The medical schools are now practically all under the control of the Universities. Nothing would be easier than for the Universities to say that after a certain date no one should enter a medical school who could not give evidence of having received sound training previously, during at least three years, in English and the elements of scientific method as applied both to the physical sciences and to biology. Assume that at first many were rejected—parents would be so angry that they would bring pressure to bear on the schools to reform their ways. Some action is needed at the moment which will bring the schools into line with the times—we may be sure that the majority will not change their ways except under compulsion.

If the student be ignorant of scientific method on leaving school, he has not merely wasted precious years: what is far worse is that he has not been disciplined as an observer and experimentalist, as a logical thinker and worker; his mental faculties will have been stunted rather than developed. Unless the art and habit of inquiry be developed in the youthful mind from the earliest days onwards, atrophy of the faculties inevitably sets in, a state of mental inertia being engendered from which it is very difficult to escape. The present system both at school and college is one from which the student receives the minimum of benefit—for the most part the training is not such as to develop scientific habits of mind.

We can apply our knowledge to secure the improvement of appliances—hence the marvellous advance of our civilisation during the past few decades; we can apply it to the study of agricultural problems—to the improvement of plants and brute animals; seemingly, however, we cannot apply it to ourselves. The reason is plain. As Mr. Francis Galton tells us in his *Inquiries into Human Faculty*:

> The vast majority of persons of our race have a natural tendency to shrink from the responsibility of thinking and standing alone; they exalt the *vox populi*, even when they know it to be the utterance of a mob of nobodies, into the *vox Dei* and they are willing slaves to tradition, authority and custom. The intellectual deficiencies corresponding to these moral flaws are shown by the rareness of free and original thought as compared with the frequency and readiness with which men accept the opinions of those in authority as binding on their judgment. I shall endeavour to prove that the slavish aptitudes in man are a direct consequence of his gregarious nature, which itself is a result of the conditions both of his primeval barbarism and of the forms of his subsequent civilisation. My argument will be, that gregarious brute animals possess a want of self-reliance in a marked degree; that the conditions of the lives of these animals have made a want of self-reliance a necessity to them and that by the law of natural selection the gregarious instincts and their accompanying slavish aptitudes have gradually become evolved. Then I shall argue that our remote ancestors have lived under parallel conditions and that other causes peculiar to human society have acted up to the present day in the same direction and that we have inherited the gregarious instincts and slavish aptitudes which have been needed under past circumstances, although in our advancing civilisation they are becoming of more harm than good to our race.

If science is to be of any value to us, it should enable us to bring influences to bear to counteract the innate peculiarities which tend to diminish human efficiency. At present, education,

as a rule, has an effect opposite to that which we desire to produce.

My proposals, it will be obvious, are far reaching. They involve, in London, the reorganisation of the University and the recognition of its Schools as dominant factors. All who are in the inner circle and who understand the working of the machine —or rather its failure to work—are aware that it comprises incompatible elements and interests: the recognised Schools, the evening schools or Polytechnics, the coaches and their following —the so-called external students. Our plain duty now is to reconstitute it as an effective organisation in which teaching can take place under conditions of maximum efficiency.

The situation is clearly foreshadowed in the following luminous lines:

"'Tis a pitiful tale," said the Bellman, whose face
Had grown longer at every word:
"But, now that you've stated the whole of your case,
More debate would be simply absurd.

"The rest of my speech" (he explained to his men)
"You shall hear when I've leisure to speak it.
But the Snark is at hand, let me tell you again!
'Tis your glorious duty to seek it!

"To seek it with thimbles, to seek it with care;
To pursue it with forks and hope;
To threaten its life with a railway share;
To charm it with smiles and soap!

"*For the Snark's a peculiar creature, that won't*
Be caught in a commonplace way.
Do all that you know and try all that you don't.
Not a chance must be wasted to-day!

"For England expects—I forbear to proceed:
'Tis a maxim tremendous but trite:
And you'd best be unpacking the things that you need
To rig yourselves out for the fight."

THE BIO-CHEMISTRY OF ANIMALS AND PLANTS

A COMPARATIVE STUDY.—I

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Chemistry, at one time intimately connected with biology, drifted away from this science during the past century, mainly owing to the apparent exhaustion of its methods in their useful application to biological problems. Meanwhile the edifice of chemistry has been perfected to such a degree that chemists are again able to attack biological questions with the help of new experimental methods. In consequence it is being more and more recognised that the sharp separation of animal and vegetable biology has only been an artificial one and does not really exist. Formerly it was held that the plant alone possessed the power of building up organic substances, *i.e.* of synthesis. The animal body, it was thought, had mainly the function of breaking down the substances supplied to it by the plant. The first synthesis taking place in the animal body was demonstrated by the classical work of Wöhler in 1824, when he showed that benzoic acid in its passage through the body was linked up to glycine and excreted as hippuric acid. Many similar instances of synthetical processes occurring in the animal body have since been found (to mention only the latest one, *i.e.* the synthesis of proteins from amino acids), and although no doubt the synthetical power of the animal organism is less than that of the plant, we know now many biological processes which are common to both.

The purpose of the following pages is to discuss in outline some of the progress made in this "Grenzgebiet" (borderland) of bio-chemistry.

The Nitrogenous Cycle

If we consider first the nitrogenous substances which play such an important rôle in the animal organism, it is evident that

they occur there in far larger proportion than in the plant, whereas the latter contains a preponderance of carbohydrates and other substances which are free from nitrogen. Here we are at the outset confronted with a fundamental difference between animals and plants, which seems to find an explanation, if we consider that the nitrogen supply of plants (apart from atmospheric nitrogen) is not at all abundant, whilst on the other hand in the carbonic acid of the air, which by the aid of the energy of sunlight they are able to transform into carbohydrates, plants possess a seemingly inexhaustible supply of carbon. Nitrogen-free carbon compounds accordingly perform functions in the plants for which there is no analogy in the animal organism, *e.g.* cellulose, in the cell membrane. It can, however, be easily demonstrated that a sufficient supply of nitrogen is one of the essential factors for plant life, and that the protoplasm of the plant contains proteins as certainly as does the protoplasm of an animal; further, that the properties and behaviour of the vegetable proteins are very nearly allied to those of animal origin.

It is a fascinating problem, which the comparative study of vegetable and animal biology has helped to solve, to investigate the great cycle of nitrogen in Nature. Here again we meet with another fundamentally important difference of animal and vegetable metabolism. The animal organism relies as the only source for its protein anabolism either on protein itself or on its direct cleavage products. It is unable to form protein material from inorganic compounds, nor does the animal cell possess the property of utilising other organic nitrogenous compounds, which have no direct relation to proteins. The animal organism, in short, depends entirely for its source of nitrogen on the vegetable world.

The raw products available to the plant for the synthesis of proteins are, mainly, the free nitrogen of the atmosphere, ammonia salts, nitrates and nitrites in the soil and organic nitrogenous substances of various kinds which are furnished by the decomposition and decay of animals and plants, such as amides, amines, amino acids, and amino salts of organic acids.

In the protein synthesis of the plant from these materials a most important rôle is played by bacteria, those micro-organisms which take an intermediate place between animals

and plants. The recognition of their importance is entirely the outcome of modern methods of investigation. This knowledge is of recent origin, and a short consideration of the main changes produced in nature by bacterial activity is essential in order to understand the nitrogenous cycle.

Nitrification.—As a final product of decay of plants or animals brought about by micro-organisms, the nitrogenous substances furnish mainly ammonia. This is transformed in the soil into nitric acid and nitrates, and enormous deposits of saltpetre have been formed in this way on the earth's surface under certain conditions. It was originally pointed out by Sir Humphry Davy that saltpetre is formed by the help of the oxygen of the air from the ammonia present in the soil, but the fact that this saltpetre formation, now usually called nitrification, is due to a biological process, carried out by the activity of microbes, has only been demonstrated in recent times. It was not until 1890 that Winogradsky succeeded in producing pure cultures of these organisms. This achievement offered great difficulties until it was found that these organisms grow best in a completely inorganic medium. They are able to obtain all their necessary carbon and nitrogen from ammonium carbonate. This nitrification process is the work of several kinds of microbes, one class called "nitrosomonas," oxidising ammonia to nitrites, and the other class, called "nitrobacter," which oxidise nitrites to nitrates. It has been shown that a large amount of organic nitrogen is transformed into nitrates in the soil and thus it is made available for the building up of the protein material of vegetable protoplasm. This is used as food for animals, and the largest amount of the protein-nitrogen of food is excreted by them in the urine, as urea or uric acid, to be transformed, also by bacterial activity, into ammonia and finally in the soil into nitrates.

Denitrification.—Whilst the nitrogenous cycle would thus appear to be a relatively simple one, another very old observation seems to break its continuity. Long ago Davy discovered that free nitrogen is formed in large quantities during the decomposition of organic substances. Towards the end of last century it was finally established that we have to deal here also with the work of microbes, which, however, work only in the absence of oxygen. This process is called "denitrification," and the organisms which are the

cause of it reduce nitrates to nitrites and ammonia, and finally to free nitrogen. So active are some of them in pure cultures that the process of nitrogen evolution resembles an alcoholic fermentation and has been aptly termed "nitrate fermentation." There cannot be the slightest doubt that by this process there is continually set free on the surface of the earth an enormous quantity of nitrogen which is apparently lost to organic life.

N-Fixation. — A solution of this apparent contradiction, although already foreseen by Berthelot, has finally been furnished and proved by the exact experimental work of Winogradsky. He succeeded in 1893 in isolating a bacillus, called by him *Clostridium Pasteurianum*, from the soil which is able to utilise directly the nitrogen of the air for building up its protein substance. A large number of similar microbes, mainly anærobes, have subsequently been isolated by other workers. That the absorption of nitrogen by these organisms takes place in large quantities is proved by experiments on trial fields, and it has been calculated that about 30 kg. nitrogen per acre are made available yearly.

This is, however, not the only way by which the atmospheric nitrogen is utilised by organic life.[1] It has long been accepted amongst farmers as a well-established fact that wheat grows better on fields on which previously leguminous plants such as clover had been grown. Biologists took no notice of this result of practical experience until quite recently. The whole process has now been completely cleared up, the work beginning with the careful investigations of Hellriegel in 1886. He was the first to establish accurately the fact that leguminous plants possess the property of absorbing atmospheric nitrogen, and he showed the connection of this property with the formation of root nodules and the presence of bacteria. To Beijerinck (1886) belongs the merit of having succeeded in isolating these bacteria in pure cultures and showing that a bacillus, called by him *B. radicicola*, enables the plant by a symbiotic process to absorb elementary nitrogen from the atmosphere and to make use of it for its growth. These

[1] An allusion might here be made to the successful modern methods of nitrogen fixation from the air by electro-chemical means (calcium-cyan-amide, calcium nitrate). As it has been stated that the saltpetre fields of Chili will be exhausted within the next fifty years, such considerations are of practical importance.

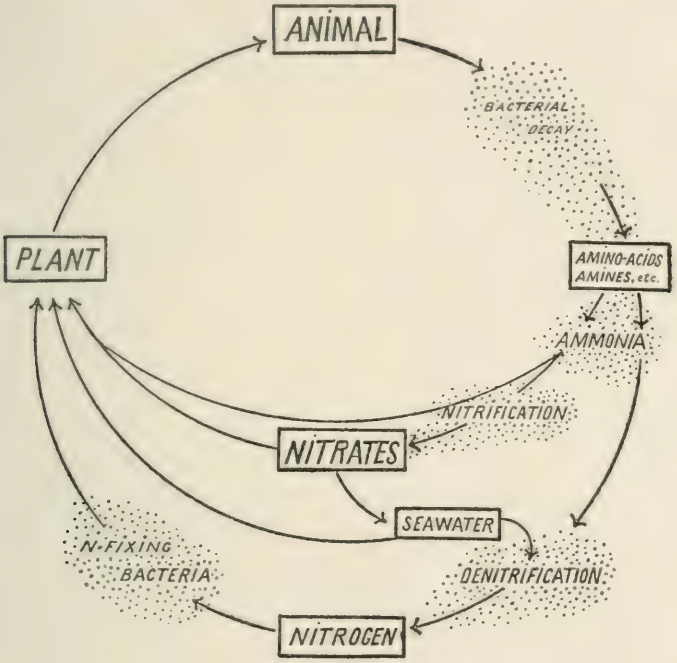
observations have been extended by Nobbe, Hiltner, Frank, Moore, and others[1] and showed that many strains of this bacillus exist and that a favourable influence on artificial infection is only noticed when cultures obtained from nearly related families are used, *e.g.* bacteria from peas will produce nodule formation in peas, but not in robinia roots. It is also interesting to note that the Japanese *Soja hispida* very often does not grow nodules in European soil, but produces them when inoculated with Japanese soil. Nothing is known so far about the initial products formed by the bacteria from nitrogen, but it is assumed that proteins are finally produced which are made use of by the plant.

Still another stage in the nitrogen cycle must be mentioned, since it helps us to understand the conditions of plant and animal life in sea-water. By the solvent agency of rain-water, soluble nitrogenous substances such as nitrates are drained out of the soil and finally carried by rivers into the sea. An enormous amount of nitrogen (Brandt calculates it at 40,000,000 gr. per annum) is thus lost to the dry land, and this is largely in excess of that nitrogen removed from the sea in the same period in the form of food fishes and other animals. The question arises, how these large quantities of nitrogen are again returned to circulation, and in this direction the discovery made by Baur in 1902 is of the greatest importance. He demonstrated the general occurrence of denitrifying bacteria in sea-water and mud. These continually throw again into circulation the nitrogen carried into the sea by the rivers, or which has accumulated there owing to the decay of plant or fish life. The discovery of the denitrifying bacteria in sea-water also helps us to solve another apparent contradiction. On the dry land the tropical and subtropical regions are more thickly populated by plant and animal life than the regions nearer the poles, whereas in the sea just the reverse is the case. In accordance with this the nitrogen content of southern warmer sea areas is smaller than that of northern colder ones. Now it has been shown that the development of the denitrifying bacteria stands in close relationship to temperature. Whilst at the temperature of the tropical seas (25–30°) the nitrogen evolution is most marked, the denitrifying bacteria are con-

[1] For a complete list of the literature from Pliny to 1901, see E. Jacobitz, *Centralb. f. Bact.* II. vol. vii. 1901, 783.

demned to inactivity at the low temperatures of 4–15° of the northern seas, and thus the nitrogenous materials are left available for plant and subsequently for fish life.[1]

We are now able to finish the picture of the nitrogen cycle in Nature, and the following schematic drawing is left to speak for itself:



THE SYNTHESIS OF PROTEIN IN PLANTS

Moulds.—The statements that some fungi (*Aspergillus* and *Penicillium* varieties) are able to fix atmospheric nitrogen like certain bacteria have so far not been sufficiently established. Moulds and yeasts, however, are able to satisfy their nitrogen want by making use of ammonia salts and nitrates. For yeasts, nitrates are less suitable than for moulds. It has further been shown that the latter synthesise their protein material still better if simple amino acids are offered to them. For one of the commonest moulds, *Aspergillus*, it was demonstrated by

[1] For a detailed account of these and similar problems, see J. Johnstone, SCIENCE PROGRESS, vol. ii. 1907, 191.

Czapek and by Emmerling that the food value of the *a*-amino acids is superior to that of all other nitrogenous substances. Abderhalden and Rona proved subsequently that this mould builds up its protein in the same way, if grown on potassium nitrate, glycine, or glutaminic acid, and that the protein thus formed in the living organism remains constant in composition, *i.e.* furnishes identical cleavage products on hydrolysis. As an explanation for this interesting observation we must assume that the *Aspergillus* starts with the amino group in the building up of its protein.

Yeasts.—A subject of considerable biological interest and at the same time of practical value is the study of the nitrogenous metabolism of yeast. To mention the name of "fusel oil" in this connection seems to be going away from the subject, but it is not really so, for the intimate association of protein formation and "fusel oil" has been made clear by the researches of F. Ehrlich, and these deserve to be referred to in some detail.

Of the various by-products of the alcoholic fermentation of carbohydrates by yeast (such as glycerin, succinic acid, ethers, aldehydes, etc.), fusel oil is the least desirable from the distiller's point of view. It was discovered by Scheele in 1785, and was shown by Pasteur to consist of higher alcohols and especially two amylic alcohols. Its smell and taste are disagreeable, and the deleterious action of certain raw spirits has, although probably without justification, been ascribed to it. The separation of fusel oil from ordinary ethyl alcohol was one of the difficulties of alcohol manufacture, which was finally solved by the perfection of fractional distillation. With the introduction of better methods, especially the use of pure yeast cultures, a distinct falling off in the quantity of fusel oil formed took place, whilst on the other hand the demand for this product for industrial processes rose to such an extent as to produce a scarcity in the world's markets. Amylic alcohol in the form of its ethers is now in great demand for the manufacture of fruit essences, celluloid, and smokeless powders. While investigating the conditions of fusel-oil formation, the view found most general acceptance that its origin was due to a bacterial decomposition of sugar. The fact, however, that the alcohols of fusel oil possess a branched carbon-chain, and that the addition of the

so-called "fusel bacteria" did not increase the output of fusel oil in normal fermentation, soon disposed of this idea.

To F. Ehrlich belongs the credit of having discovered the exact conditions for the production of fusel oil, and its close connection with protein synthesis from amino acids in the growing yeast cell. The application of the results of modern researches on protein constitution, and the amino acids produced by its cleavage, led him to this solution. He discovered iso-leucine in molasses as well as in yeast, and as a constant proteolytic cleavage product of other proteins (fibrin, caseinogen), and this, together with the general occurrence of amino acids in plant juices and the similarity in constitution of leucine to iso-amylic alcohol, led him to the view that amylic alcohol and its homologues are produced from amino acids by the agency of yeast itself. The conclusive proof for the correctness of this view was the discovery that the fermentation of these amino acids by means of pure yeast cultures occurs in the presence of sugar. In this way Ehrlich succeeded in obtaining iso-butyl alcohol from valine, iso-amylic alcohol from leucine, and d-amylic alcohol, the only optically active constituent of fusel oil, from iso-leucine in quantities corresponding to the amount of amino acid which he had added. Whilst the highest percentage of fusel oil of raw spirit was formerly 0·5 per cent., it is now possible by these means to increase it ten to twelve times.

The formation of the higher alcohols from the amino acids admits of a very simple chemical explanation. With the addition of water a simultaneous splitting off of CO_2 and NH_3 takes place, as expressed by the following formulæ[1]:

leucine.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!\rangle CH \cdot CH_2 \overset{*}{C}H \cdot (NH_2) \cdot COOH + H_2O =$$

iso-amylic alcohol.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!\rangle CH \cdot CH_2 \cdot CH_2OH + NH_3 + CO_2$$

iso-leucine.

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!\rangle \overset{*}{C}H \cdot \overset{*}{C}H(NH_2) \cdot COOH + H_2O$$

d-amylic alcohol.

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!\rangle \overset{*}{C}H \cdot CH_2 \cdot OH + NH_3 + CO_2$$

During the growth of the yeast cell these reactions probably

[1] $\overset{*}{C}$ = asymmetrical carbon atom.

take place by means of an enzymatic action, and the ammonia is directly used up for the formation of protein. The fusel-oil formation depends not only on the amount of amino acids, but also on the kind and quantity of other nitrogenous substances present. In the presence of easily assimilated nitrogen, such as asparagine or ammonium salts, practically no fusel oil is formed. Ehrlich has also applied this process for the preparation of optically active amino acids from the racemic inactive compounds, one component only being transformed into the corresponding alcohol. But not only is yeast able to use leucine and iso-leucine as a source of nitrogen for its protein formation, but also all the other *a*-amino acids, *e.g.* tyrosine is converted into p-oxy-phenyl-ethyl alcohol, and phenyl-alanine furnishes phenyl-ethyl alcohol. The formation of this latter substance, which represents the largest bulk of the essential oil of roses, opens a new outlook for another branch of plant physiology, the formation of essential oils and their connection with proteins.

Carnivorous Plants.—Of great interest is the existence of plants which secrete products analogous to the digestive juices of animals, and which are able to digest insects or proteins. This great group of carnivorous plants comprises *Drosera*, *Pinguicula*, and *Utricula* varieties, etc. The various kinds of *Nepenthes* act on a larger scale, catching and digesting insects by means of the liquid in their pitchers. It is still doubtful whether the action of these enzymes corresponds to that of pepsin or trypsin, although some recent preliminary experiments by Abderhalden and Terunchi make it probable that it is not of a trypsin nature. They found that the dipeptide glycyl-l-tyrosine is a very convenient substance to distinguish between pepsin and trypsin, as it is not attacked by the former, but easily split into its components by the latter. The juice of *Nepenthes* has no appreciable action on this dipeptide. Recently Vines has succeeded in showing that an enzyme of the nature of erepsin occurs largely in plants and also to some extent in *Nepenthes* pitchers. This enzyme was originally discovered by Cohnheim in the intestinal mucous membrane, and it was shown by Vernon to be generally present in all animal tissues. It has no action on proteins as such, but splits peptones, albumoses, and polypeptides into amino acids. One would expect that the carnivorous plants would be able to

use amino acids themselves or higher cleavage products for their protein synthesis. There has been very little work done on the metabolism of carnivorous plants, and this point has not been investigated. That plant organisms exist which produce their protein from the higher cleavage products alone has, however, been made clear by the researches of Beijerinck, who proved that the alga living symbiotically with *Physcia parietina* requires peptones (*i.e.* albumoses) for its normal growth.

Higher Plants.—Relatively little is yet known about the protein synthesis in plants containing chlorophyll. The study of the processes occurring during germination has attracted many investigators, and has furnished most useful results. The ripe seeds nearly always contain a large store of protein. As soon as germination begins great changes take place in cells. The proteins are decomposed by the action of proteolytic ferments, the existence of which, during germination, has been definitely proved. By the action of these ferments the higher cleavage products first obtained from the proteins are finally converted into simple amino acids, which are partly at least made use of at once by the growing plant. We may compare the process of germination with that occurring during digestion in the animal body. In both cases the complex food protein is first decomposed into simpler cleavage products, and it is from these that the organism reconstructs the protein matter of its protoplasm. A long series of amino acids, leucine, tyrosine, aspartic acid, glutaminic acid, arginine, lysine, histidine, etc., have been isolated from germinating seeds. A peculiar occurrence is the formation of asparagine and sometimes of glutamine, substances which have not been observed in any artificial protein hydrolysis. By allowing seeds to germinate in the dark, *i.e.* under normal conditions, large amounts of these two substances may be produced. The significance of asparagine formation is not yet fully understood. Pfeffer has shown that the increase of the asparagine is coincident with the decrease of carbohydrate formation in the absence of light, which stands in close relationship to the protein synthesis, the absence of which entails an accumulation of amino acids. It is possible that asparagine represents a transition stage in the formation of other nitrogenous substances, or perhaps that it is connected with carbohydrate and fat formation. This view is confirmed by certain observations made upon tyrosine. This amino acid

is produced in large amounts during the initial stages of the germination. By the action of a ferment, which can easily be localised, it is, however, very quickly converted into a nitrogen-free substance—homogentisinic acid. This same substance, by the way, is formed from tyrosine in the human body under certain abnormal conditions and excreted in the urine, giving rise to so-called alkaptonuria.

After the exhaustion of the nitrogen supply from the seed, the plant depends for its nitrogenous foods on the nitrates and ammonia salts of the soil. Those plant organs seem to be predestined to carry out the protein synthesis in the adult plant, in which carbohydrate formation is also most vigorous; and it was pointed out by Sachs in 1865 that the leaves perform the largest share of this work. Very little definite knowledge exists with regard to the actual processes. It is generally accepted now that the first substances formed are amino acids, and that by the linking of these together into complex chains the proteins are ultimately produced. Light plays a most important part in the protein formation in leaves. Whilst leaves are unable to make use of free nitrogen, several observations confirm the view that small amounts of ammonia are absorbed. The protein synthesis in leguminous plants, which takes place by the help of bacteria, has already been discussed (p. 679).

Protein Synthesis in the Animal Organism

Since Loewi's experiments, which showed that in animals weight, health, and nitrogenous equilibrium can be maintained for a considerable time by feeding them on the crystalline cleavage products of protein hydrolysis, the old view that the albumoses and peptones are absorbed as such has been steadily losing ground. The belief is now general that the largest part of the ingested protein undergoes cleavage into its fundamental amino acids, and that the body exerts a selective power in building up its various proteins from these comparatively simple materials. Evidence is accumulating which confirms this view, and of the many researches in this direction, those of Abderhalden and his collaborators should be specially mentioned.[1]

[1] This question has been fully discussed by F. G. Hopkins, Science Progress, vol. i. 1906, 159, and by E. P. Cathcart, *ibid.* vol. ii. 1907, 76.

The Vegetable Proteins

The preponderance of carbohydrates in plants explains the fact, shown in the history of plant physiology, that the general occurrence of nitrogen in plants has been recognised relatively late, and that the presence of proteins especially has been considered as an exceptional occurrence.

History.—From an historical point of view it is interesting to note that the earliest known vegetable protein was wheat gluten; this was isolated by Beccari in the eighteenth century. Berzelius examined it at the beginning of last century and called it "vegetable glue" or "vegetable casein" on account of its similarity to the corresponding animal substances. Braconnot isolated about the same time the proteins of peas and beans, which he called "legumin." Gay-Lussac subjected vegetable proteins to elementary analysis, and was the first to point out the general occurrence of proteins in seeds. But Liebig and his pupils were the real founders of the system which led to our modern knowledge of protein chemistry. He distinguished between plant albumin (coagulated by heat, not precipitated by acids), plant casein (not coagulated by heat, not precipitated by acids), and plant fibrin. The view also originated from his laboratory that elementary analyses of proteins teach us very little about the nature of these substances and that more knowledge is obtained by the investigation of their hydrolytic cleavage products. The classical work of Ritthausen, published in 1872, was the outcome of the application of these methods to vegetable proteins. Ritthausen's work still remains of importance, although his methods have been superseded by the introduction of neutral salts for the purpose of isolation and separation of proteins. The names of Hoppe-Seyler, Weyl, Schmiedeberg, must be mentioned in this connection. It was mainly Kühne's pupil, Chittenden, and later Osborne, two American workers who applied the method of fractional salt precipitation to vegetable proteins. This method is still a valuable one, and it is to be hoped that together with the latest processes for the isolation of hydrolytic cleavage products, which we owe to the genius of E. Fischer, we shall be able in the near future to form clearer ideas of the constitution of proteins.

Occurrence and Properties.—With regard to most of the

proteins of leaves and roots we are ignorant of the state in which they are present in the cell sap and the cell protoplasm, and indeed in most cases the proteins of the fully grown plant have received but little attention. The best-known vegetable proteins are those which occur stored up in the seeds as "reserve" food for the growing organism, and they show many analogies with the corresponding animal proteins. As a rule they resemble in their chemical and physical behaviour the animal globulins, *i.e.* they are insoluble in water, but soluble in salt solutions and precipitated by dilution or by removal of the salts by dialysis. They crystallise very often inside the cell itself and they were the first crystallised proteins known (Hartig, 1853). Protein crystals are found especially in the endosperm of oily seeds, in the so-called "aleurone" grains (especially of the Para nut, castor-oil seed, etc.). From their solutions they can again be obtained in a crystalline form by relatively easy means. The methods introduced by Hofmeister for the crystallisation of egg albumin have not yet been applied to vegetable proteins. It is a remarkable fact that whilst the vegetable globulins crystallise most easily, the animal globulins have not yet been obtained in crystalline form.

Most of the vegetable proteins, however, like those of the animal body, are characterised by their colloidal nature. Still, numerous transition stages between the colloid and crystalloid condition are also found; thus many vegetable proteins are soluble in alcohol, have lost their property of being coagulated by heat, and have a diminished viscosity. The vegetable proteins examined so far are all lævo-rotatory.

Constitution of the Protein Molecule. Protein Hydrolysis.— Elementary analysis and the study of the physical properties and chemical reactions of the animal and vegetable proteins have led to their classification into more or less well-defined groups. These are subdivided according to purely external characteristics, such as origin, solubility, coagulability, etc. On the basis of such properties we distinguish to-day some forty to fifty natural proteins, and this number will probably increase as the methods of differentiation are improved. A better knowledge of the probable constitution of the protein has, however, resulted from the attempts to study systematically their cleavage products. The means which were made use of to obtain this end were the action of enzymes, of acids and alkalies in varying

proportions, of water under increased pressure, of oxidising and reducing agents, etc. Of all these methods two have led to the most constant and useful results—namely, hydrolysis by means of ferments and by dilute mineral acids—and these methods play at present a most important rôle in protein chemistry. Whilst the last method has led to a knowledge of the final cleavage products, the intermediate substances, which still show protein characters, have been made available for further study by the use of enzymes. The well-known stages of enzyme action are the albumoses or proteoses, the peptones and amino acids. Only quite recently E. Fischer has demonstrated an intermediate stage between the peptones and the amino acids by the isolation of the so-called polypeptides, which promise to be of the highest importance for the chemistry and biology of the proteins.

The ideal aim of the chemist would be to separate the complex mixture of cleavage products quantitatively in such a way as to account for the whole of the carbon, nitrogen, and sulphur in the original protein. This idea will, however, probably never be attained on account of the secondary reactions taking place during hydrolysis, such as formation of brown and black pigments, splitting off of CO_2, etc. Even with the best methods at his disposal, E. Fischer has succeeded so far only in separating at the utmost 50 to 70 per cent. of the amino acids present in the cleavage products.

Under these circumstances it is of the greatest value to be able to obtain by a short and reliable procedure at least an approximate knowledge of the nitrogen distribution in the protein molecule, even if this does not allow us to determine quantitatively the single cleavage products. Such a method has been worked out, mainly in Hofmeister's laboratory, by Hausmann, and has been subsequently found trustworthy by Osborne and others.

Hausmann's method is shortly as follows : The whole nitrogen of the protein is estimated by Kjeldahl's method. A weighed amount of the substance is then hydrolysed by means of hydrochloric acid. After complete hydrolysis the cleavage products are separated into three classes, and the nitrogen estimated in each by means of Kjeldahl's method as—

1. Amide-N or ammonia nitrogen. This comprises the nitrogen of that part of the protein molecule which is easily

split off as ammonia, and is determined by distilling off the ammonia with magnesia.

2. Diamino-N. The fluid, free from ammonia, is precipitated by phosphotungstic acid, and the nitrogen present in the precipitate determined. This represents the nitrogen of most of the diamino acids, such as histidine and arginine.

3. Monoamino-N is estimated in the residual fluid after removal of the amide and diamino-N.

Although this method is not absolutely correct, it has nevertheless furnished most valuable information when applied to different animal and vegetable proteins, as is shown in the following table from the analyses of Osborne:

	Total N.	Amide-N.	Diamino-N.	Monoamino-N.
Zein (maize) . .	16·13	2·97	0·49	12·51
Hordein (barley) .	17·21	4·01	0·77	12·04
Gliadin (wheat) . .	17·66	4·20	0·98	12·41
Glutenin (wheat) .	17·49	3·30	2·05	11·95
Globulin (wheat) .	18·39	1·42	6·83	9·82
Leucosin (wheat) .	16·93	1·16	3·50	11·83
Edestin (hemp) . .	18·64	1·88	5·91	10·78
Excelsin (Para nut) .	18·30	1·48	5·76	10·97
Caseinogen (milk) .	15·62	1·61	3·49	10·31

These figures show interesting differences between otherwise similar proteins. New characteristics are given for some protein groups, *e.g.* the alcohol soluble vegetable proteins, which possess a high amide-N and low diamino-N. In Osborne's analyses (not given) of various so-called edestins, great differences of the diamino-N was revealed. The method has also proved useful for the differentiation of albumoses (Pick), and interesting deductions as to the food value of various proteins were drawn from its results (Blum). As 80 to 90 per cent. of the carbon of proteins (according to Kossel) is present in combination with nitrogen, the method is likely to give important clues as to the constitution of different proteins.

Cleavage Products.—The following is a list of the main substances so far met with among the hydrolytic products of proteins; they are classified roughly under the divisions of Hausmann's method, and in each case the constitutional name and discoverer of these substances are given:

Monoamino-N

Glycine (amino-acetic acid, Braconnot 1820).
Alanine (amino-propionic acid, Weyl 1888).
Valine (amino-valerianic acid, Gorup-Besanez 1856).
Leucine (amino-caproic acid, Proust 1818).
Iso-leucine (amino-caproic acid, Ehrlich 1903).

Serine (oxy-amino-propionic acid, Cramer 1865).
Phenylalanine (phenyl-amino-propionic acid, Schulze and Barbieri 1881).
Tyrosine (oxy-phenyl-amino-propionic acid, Liebig 1846).
Tryptophane (indole-amino-propionic acid, Hopkins and Cole 1901).

Aspartic acid (amino-succinic acid, Plisson 1827).
Glutaminic acid (amino-glutaric acid, Ritthausen 1866).

Proline (pyrrolidine carboxylic acid, Fischer 1901).
Oxyproline (oxy-pyrrolidine-carboxylic acid, Fischer 1902).

Diamino-N

Ornithine (diamino-valerianic acid, Jaffe 1877).
Lysine (diamino-caproic acid, Drechsel 1889).
Arginine (amino-guanidine-valerianic acid, Schulze and Steiger 1886).
Histidine (amino-imidazole-propionic acid, Kossel 1896).
Diamino-trioxy-dodecanic acid (Fischer and Abderhalden 1904).
Cystine (diamino-dithio-d-lactic acid, Wollaston 1810).

The proportions in which the various amino acids are obtained from different proteins vary considerably. The quantitative examination of various proteins, by the help of the methods introduced by A. Kossel and E. Fischer, is being carried out at present in many laboratories, and has already furnished most valuable results, *e.g.* albumins are distinguished from globulins by their complete lack of the glycine group, whilst on the other hand gelatin furnishes as much as 17 per cent. of this substance. The latter protein, however, does not yield

any tyrosine or tryptophane. The alcohol-soluble vegetable proteins are characterised by their complete lack of glycine and lysine, and are especially rich in glutaminic acid (gliadin of wheat containing 36 per cent.). Some animal proteins, such as the protamines, yield enormously high percentages of arginine (salmine = 84 per cent.). It is worth noting in this connection that in the hydrolysis of all important proteins which play the chief part in animal or vegetable metabolism, all these amino acids occur almost without exception, so that the conclusion must be drawn that none of them can be dispensed with in organic life.

Synthesis.—The study and isolation of the hydrolytic cleavage products have thus been shown to be of the greatest importance. As the same substances are not only formed by the action of acids and alkalies, but also by the agency of the digestive enzymes, they are to be regarded as the true "Bausteine" (building stones), of which the complicated protein molecule is built up. Starting from this idea E. Fischer has been able to build up, by linking together simple amino acids (a process the reverse of hydrolysis), substances which he called polypeptides. These are very similar to the polypeptides which he isolated from digestive mixtures, and even some of the relatively simple ones, such as l-leucyl-triglycyl-l-tyrosine, exhibit many of the properties of the albumoses. The octa-deca-peptide derived from fifteen molecules of glycine and three molecules of leucine, having the high molecular weight of 1213, is a substance which, in its external properties, closely resembles many natural proteins. More than one hundred of these artificial polypeptides have already been synthesised, and we may expect in the near future the announcement of the synthesis of what E. Fischer regards as the simplest protein, namely silk-fibroin, which according to his researches only contains four different amino acids.[1]

Classification of Vegetable Proteins.—The classification of the proteins in general is at present under revision, and can only be a provisional one in view of the rapid progress being made in their chemistry. It is possible that shortly the increased knowledge of the cleavage products and their quantitative

[1] For a complete account of Fischer's work see his book, *Untersuchungen über Aminosäuren, Polypeptide und Proteïne*, 1906; also R. H. Aders Plimmer, SCIENCE PROGRESS, vol. ii. 1907, 88.

relationships will produce an important change in our present classification. With regard to the vegetable proteins, this is all the more desirable, as they can only be fitted in with difficulty into the present system. A complete up-to-date treatise[1] of the vegetable proteins has still to be written, and their nomenclature and classification are at present in a most unsatisfactory and perplexing state. For the purpose of this paper the material to be dealt with has been divided into four main classes, it being recognised, however, that this classification can only be a tentative one, and open to criticism.

The following classes are proposed:

1. Phyto-albumins.
2. Phyto-globulins.
3. Gliadins (alcohol-soluble proteins).
4. Phyto-caseins (phyto-vitellins).[2]

1. The proteins of the first class are the least known of vegetable proteins, the reason for this being that the seeds, which form the main source for the study of plant proteins, contain albumins only in relatively small proportions. Many observations show, however, that they are also present in leaves and the cell-sap of other parts of plants.

The vegetable albumins possess the same characteristics as those of animal origin. They are soluble in water and salted out by ammonium sulphate and other salts. They require a larger amount of salt for their precipitation than the globulins. They may be separated from the latter by dialysis, remaining in solution after the removal of the salts. They have not yet been obtained in a crystalline form, are coagulated by heat, and show all the typical colour reactions of the proteins. They are phosphorus-free.

The best known of the vegetable albumins is a substance called *leucosin*. It occurs in small quantities in grasses, but has been prepared mainly from wheat grains (also rye, barley, and maize), in which seeds it is present to the extent of 0·3—0·4

[1] Only two exhaustive treatises exist on vegetable proteins: *Die Eiweisskörper der Getreidearten*, etc., Ritthausen, 1872; and *Die Proteide der Getreidearten*, etc., Griessmayer, 1887. The latter is a translation of Chittenden and Osborne's collected older papers.

[2] The name "Glutelin" has recently been proposed by a committee of the American Physiological Society for these substances.

per cent. For its preparation the seeds are extracted with water or dilute salt solutions, the whole of the dissolved proteins precipitated by saturation with ammonium sulphate, and a solution of the precipitate subjected in dialysis. The globulins become insoluble with the removal of the salt, and from the remaining aqueous solution leucosin may be precipitated in the usual way. It is coagulated at a temperature of 52°; this is lower than the heat-coagulating point of the corresponding animal albumins. It contains 16 per cent. N. and 1·5 per cent. S. and on hydrolysis it furnishes nearly four times as much mono-amino-N as diamino-N.

2. *The Phyto-globulins.*—The best-known vegetable proteins belong to this class, and they represent the main reserve proteins of the seeds. Their properties are so much like those of the animal proteins that they have been considered by Chittenden and Osborne—to whom we are mainly indebted for our knowledge about them—as directly analogous to the animal globulins. The ease with which many of them assume a crystalline form, however, distinguishes them from the animal globulins. It is true that lately a doubt has been expressed by Wiman as to their globulin character, as he found 0·4 per cent. phosphorus in legumin, the globulin of peas. But Osborne upholds his view that the purified substances must be considered as phosphorus-free real globulins. Only phosphorus-free proteins ought to be included in this class.

The best-known representative of this class, and one which, on account of its easy preparation, has been most thoroughly examined, is *edestin*. It seemed from their properties and composition that the various crystallised globulins called edestin, and obtained from the seeds of wheat, oat, maize, sunflower, cucumber, cotton, flax, and hemp, represent all one and the same substance. But the analysis by Hausmann's method, carried out by Osborne and Harris, revealed distinct differences in their molecular constitution. Edestin is easily prepared in large quantities from hemp-seed, which contains about 6—8 per cent. edestin. The seeds are first treated with benzene, to remove the oil, then extracted with 5 per cent. salt solution at 60° C., and filtered warm. On cooling, edestin crystallises out, and may be easily recrystallised in the same way. It usually forms well-defined octahedra, but on slow crystallisation prismatic crystals may be obtained. Its insolubility in water distinguishes

it from the albumins; it is, however, easily soluble in salt solutions, and gives most of the usual protein tests. It contains 18·5—18·8 per cent. N and 0·8—0·9 per cent. S, and is phosphorus-free. Its heat-coagulation temperature is at about 90°, much higher than that of the animal globulins. Abderhalden has recently examined its cleavage products.

Another very well-crystallised globulin of this class is the protein of the Para nut (*Bertholletia excelsa*), which has been called *excelsin* by Osborne. It occurs in a crystalline form in the aleurone grains in the endosperm of this fruit, and can be easily obtained as hexagonal crystals in a similar way to that described for edestin, which it resembles in character and composition. Its hydrolytic cleavage products have recently been isolated by Osborne and Clapp. A striking feature is the unusually large proportion of arginine found (16 per cent.). A very similar protein has been obtained by Osborne in a crystallised form from oats, and called by him *avenalin*.

The proteins of leguminous plants have been fairly well examined, and must be included in this class. The globulin of beans, which is called *phaseolin* (discovered by Ritthausen), amounts to about 20 per cent. of the seeds, which contain also about 2 per cent. of a second globulin of a greater solubility called *phaselin*. They contain less nitrogen and sulphur than edestin and excelsin. The globulin of peas is called *legumin*. It is not precipitated by sodium chloride or magnesium sulphate on saturation, and gives a rose-red biuret reaction, like peptone. It is also only partially coagulated by heat. The mono-amino-acids of its hydrolytic products have been examined by Abderhalden and Babkin, and these are very similar to those obtained from *conglutin*, the protein isolated by Ritthausen (and subsequently studied by Osborne) from lupins. The name of conglutin had formerly been given to a series of proteins isolated from almonds, peach kernels, walnuts, etc. Osborne and Campbell showed that these proteins differed from conglutin, and accepted the name "amandin" originally given by Proust, for the protein of almonds and peaches. The protein of the hazel nut (*Corylus*) has been called *corylin* by Osborne and Harris. This differs from the globulin of walnuts (*Juglans*), which has been termed *juglansin* by the same observers, in containing more amide-nitrogen, and in being less readily precipitable by ammonium sulphate. For the separation and

distinction of these and other vegetable proteins, fractional precipitation by ammonium sulphate (introduced by Hofmeister) and the application of Hausmann's method proved most useful.

3. *The Alcohol-soluble Proteins.*—The substances belonging to this class, for which the general name *gliadin* is proposed, and which possess no direct analogues amongst the animal proteins,[1] are characterised by their unusual property of being easily soluble in dilute alcohol, some even being soluble in 96 per cent. alcohol. Ritthausen was the first to point out that the seeds of wheat, rye, barley, maize, and oats contain proteins which are insoluble in water and salt solution, but readily soluble in alcohol. In wheat these substances, together with the insoluble phyto-casein (glutenin), form the so-called gluten, the adhesive glue-like material, which is of the greatest importance in bread-making, by giving the necessary tenacity to dough. The chemical characteristics of this class are the high amount of glutaminic acid and the absence of glycine and lysine in their cleavage products. Only three substances of this class have so far been studied to any degree. They are called *wheat gliadin*, *zein* (from maize), and *hordein* (from barley).

Wheat Gliadin.—Ritthausen originally distinguished three alcohol-soluble substances in wheat which he called gliadin (plant glue), glutenfibrin, and mucedin. He was, however, unable to separate them quantitatively, and subsequent investigators, especially Osborne and Campbell, returned to the old view of Taddei's that there is only one alcohol-soluble substance, for which they retained the name of *gliadin*. It seems, however, preferable to call it wheat gliadin in distinction from the group name. It is identical with the substance obtained from rye, and amounts to 4 to 5 per cent. of the grain. It is insoluble in absolute alcohol, but easily soluble in 70 to 80 per cent. alcohol, and is precipitated from these solutions by the addition of water. It is especially characterised by the high percentage of glutaminic acid, which it furnishes on hydrolysis, amounting to 36 to 37 per cent., and the total absence of lysine among its cleavage products. On account of the strikingly different percentages of cleavage products from those of animal proteins, it was chosen by Abderhalden

[1] Pick suggests a similarity to the proto-albumoses.

and Samuely for an interesting experiment with regard to the synthesis of proteins in the animal body. These observers found that on administering it to a horse which had previously lost a large amount of blood, the composition of the serum proteins remained constant.

The alcohol-soluble protein of maize was called *zein* by Gorham, and subsequently maize-fibrin by Ritthausen. Osborne and Chittenden reinvestigated this substance and retained the name zein. It is characterised by its solubility in even strong alcohol of 96 per cent., and its complete insolubility in water. Glutaminic acid is also present in large quantities among its cleavage products, and lysine is absent. The indole-molecule (tryptophane) is also missing, and zein represents, therefore, a convenient material to investigate the question how far the absence of certain cleavage products influences the nutritive value of a protein. Hopkins and Willcock found that growth was very favourably influenced in young animals by zein and tryptophane, whilst zein itself was insufficient.

Hordein is the name given by Osborne to the alcohol-soluble protein of barley. Its differs somewhat from wheat gliadin in its solubilities, and contains more carbon and less sulphur than the latter. The hydrolytic cleavage products, examined by Osborne and Clapp, resemble quantitatively those of the other gliadins. Lysine is absent, and as much as 41 per cent. glutaminic acid was found. The most marked feature, however, is presented by the very large percentage of proline (pyrrolidine-carboxylic acid), which exceeds that yet obtained from any other protein, being practically 14 per cent., or twice as much as that yielded by wheat gliadin.

4. *The Phyto-caseins (or Phyto-vitellins).*—These substances are found in maize, barley, rye, and wheat, and amount in some cases to nearly 50 per cent. of the total protein. When these seeds are completely extracted by treatment with water, followed by salt solution and subsequently alcohol, the residue still contains a large amount of protein, which can only be extracted by treatment with very dilute (0·2 per cent.) alkali. From this solution they are precipitated by neutralisation with acids. They are insoluble in water and alcohol, but show both acid and basic properties, being easily soluble in a slight excess of alkali or acid. The question of their per-

centage of phosphorus has not yet been definitely settled. It may be mentioned here that, according to the unpublished results of an investigation carried out by Dr. Kajiura and the author on the proteins of rice, this cereal also contains a similar substance, which forms the bulk of the rice proteins. Curiously enough, although rice forms the staple food of Oriental races, its proteins have not until now been examined.

The best-known representative of this class is *glutenin*, the alcohol-insoluble part of gluten of wheat. This substance may be easily prepared by the method explained above. In distinction from its constant companion, the wheat gliadin, it furnishes only 9 per cent. glutaminic acid, and contains 2 per cent. lysine amongst its cleavage products. The main interest consists in its connection with gluten-formation. There is still some uncertainty about the process of gluten-formation and the conditions regulating it. The question is an important economic one, as it is intimately connected with the "strength" of flour—*i.e.* the property of wheat which makes it pre-eminently suitable for bread-making.[1] The stiff coherent mass which is formed when wheat-flour is mixed with cold water owes its formation to the presence of proteins, for no such action takes place when pure wheat-starch is mixed with cold water. The question arises whether the gluten proteins exist pre-formed in the grain, or whether they are produced by a secondary change. Weyl and Bischoff compared this process to fibrin formation from fibrinogen in the coagulation of blood, and they assumed the existence of a ferment which transforms in the presence of water the gluten-forming substances into gluten. They were, however, unable to demonstrate such a ferment, and the experiments of Osborne and Voorhees, although they do not exclude ferment action altogether, seem to prove that gluten is formed by the chemical or physical interaction of its two constituents—the gliadin and glutenin. Attempts have been made to explain the relative "strength" of flour from wheat and other cereals by the quantitative relationship of glutenin to gliadin. It seems, however, to be more likely to depend on the physical state of the gluten, which is, as already shown by Ritthausen and Osborne, dependent on the presence of mineral salts.

[1] See A. E. Humphries, SCIENCE PROGRESS, vol. ii. 1907, 175.

It might be mentioned finally that, amongst the vegetable proteins, albumose-like substances have also been met with, but their existence as such in seeds is doubtful. Small quantities of peptones have also been observed.

Typical nucleo-proteins occur in plants. The nucleic acid, isolated by Kossel from yeast, was the first substance of this type known. Osborne and Harris have lately isolated and investigated very thoroughly a nucleic acid from wheat embryos. It furnishes characteristic purine bases on hydrolysis.

(To be continued)

REVIEWS

Textbooks of Physical Chemistry: Stoichiometry. By SYDNEY YOUNG, D.Sc., F.R.S. Also an "Introduction to the Study of Physical Chemistry," by Sir William Ramsay, K.C.B., F.R.S., Editor of the Series. [Pp. lxi. + 381.] London: Longmans, Green & Co. *7s. 6d.*

NEARLY four years have elapsed since the first of these textbooks was issued. In that first volume the hope was expressed that the others of the series would be ready for the press before the end of 1904. This hope has not been realised; but so long as slight delay secures excellence of workmanship, and so long as the contents of each volume are brought up to date, one is prepared to cease grumbling and give a hearty welcome to each belated arrival.

In the case of two of the previous volumes there was just ground for complaint of the excessive bulk and price; treatises on Spectroscopy and Stereochemistry extending to 500 or 600 pages are really quite beyond the limits of a textbook, and out of proportion to the scale of the earlier volumes of the series.

It is therefore gratifying to find that Professor Young, notwithstanding the fundamental and extensive character of his subject, has contrived to give an excellent presentation of it within a reasonable compass. In gauging the extent of the ground which he has to cover, it must be remembered that "stoichiometry" means a good deal more nowadays than it once did. Although not a very common word, it is more than a century since it was first used by Richter to denote the determination of the proportions in which substances combine. Subsequently the meaning has been extended to comprehend not only the determination of atomic and molecular weights, but also the study of the general properties of gases, liquids, and solids, the behaviour of mixtures, solubility, the properties of dilute solutions, and other kindred subjects.

On the relationship between the gaseous and the liquid states, and on cognate problems, Professor Young is especially qualified to write, in virtue of his own extensive and admirable investigations, but in the other parts of the book also the treatment is generally good. A critical perusal of the two chapters on the determination of atomic weights may be recommended, for much loose thinking on this subject is current even among advanced students.

As regards the division of the available space among the various sections of stoichiometry, and as regards the arrangement of the chapters, there is some room for criticism. Only twenty-four pages are allotted to the consideration of the properties of dilute solutions—a space which, in view of the part played by dilute solutions in the development of modern physical chemistry, is decidedly inadequate. When this small space is compared with the 130 pages devoted in a previous volume to the subject of steric hindrance it is obvious that the scale of treatment by the different authors of the textbooks has been very far from uniform.

The chapter on the properties of dilute solutions not only suffers from undue brevity; in one respect, at least, it has not been brought up to date. The last

few years have witnessed a remarkable advance in our experimental knowledge of osmotic pressure—an advance chiefly due to Lord Berkeley and Mr. Hartley, on the one hand, and to Messrs. Morse and Frazer, on the other. The work of the latter investigators is of the utmost importance, involving an extension to concentrated solutions of van 't Hoff's formula for dilute solutions. In Professor Young's discussion of osmotic pressure, however, no reference is made to Morse and Frazer's work.

In regard also to the arrangement of the chapters a word of criticism may be permitted. To devise an arrangement which should be universally acceptable is perhaps a vain hope, but it does seem curious that a chapter on "The Dissociation of Gases and Vapours" should be placed between one on "The Periodic Law" and one on "The Properties of Liquids." The author may have a good reason for this arrangement, but it would seem more rational to discuss cases of abnormal vapour density in that portion of the book which deals with the molecular weights of gases and vapours. Again, the insertion of a discussion of the kinetic gas theory between chapters on the properties of liquids and the properties of solids is open to criticism. It is no doubt true that this theory is closely connected with van der Waals' equation of state, but it should be discussed primarily in relation to the experimental gaseous laws. The three gaseous laws which must be regarded as fundamental by the physical chemist are (1) Boyle's Law, (2) Gay Lussac's Law, (3) Gay Lussac's Law of Volumes, and the descriptive exposition of these should be followed immediately by a discussion of their theoretical basis in the kinetic gas theory and Avogadro's hypothesis.

But although there thus appears to be some ground for criticism, Professor Young's volume may be cordially commended to all those who seek to familiarise themselves with the point of view of physical chemistry—a point of view which is both rational and stimulating.

J. C. PHILIP.

Physiography. By ROLLIN D. SALISBURY, Professor of Geology and Head of the Department of Geography in the University of Chicago. London: John Murray. 1907.

IN this country the term physiography is applied by the Board of Education to an assemblage of theoretical and experimental material, gathered from nearly every branch of science, to form a subject for instruction and examination in our elementary schools. In the United States, on the other hand, it is employed with a more definite meaning and concerns itself with the physical aspects of our planet and their variations in time and space. It is a favourite study in the higher classes in schools, and lower classes in colleges, and the present volume is one of the best that has appeared in recent years to satisfy the demand for a text-book on the subject. Its most striking characteristic is its wealth in illustration. Every stage in the evolution of the land is depicted in clearly reproduced photographs of American scenery; the diagrams are striking, and in many cases original; but a still more important feature is the number of maps. These include effective photographs from models, graphic representations of the distribution of physical phenomena, and transcripts and facsimiles of the topographical maps of the United States Geological Survey. These last are closely contoured, and give an excellent idea of the form of the earth's surface. One is glad to be reminded by the author that the originals can be obtained from the Director of the Survey at Washington at the rate of three dollars a hundred, which works

out at about three-halfpence each. The author is to be congratulated on the fact that he has in every case restricted his maps and diagrams within the limits of the format of the book, thus avoiding the inconvenience of folded sheets.

Though showing occasional traces of haste, the text is as a rule clear and readable, besides containing much that is suggestive and original. Perhaps the least satisfactory portion of the book is that which deals with the regional distribution of pressure in high latitudes, the explanations that are offered being hardly calculated to carry conviction to the mind of the student. It is true that much remains to be done in working out the details of the subject ; but the main principles admit of very simple expression. Briefly, the variations in pressure on the earth's surface are dependent on differences of temperature, moisture, and centrifugal force—to use a useful term by no means free from objection but sufficiently well understood. The tendency of heat alone would be to make the pressure increase continuously from the equator to the poles. That of centrifugal force alone has exactly the contrary effect, for air moving towards the poles has a greater rotational velocity than that proper to its new latitude, and therefore tends to rise, while air moving towards the equator tends to sink. The magnitude of this effect is dependent on the rate of change in the length of the radius of rotation, a rate which increases rapidly as the pole is approached. Thus it comes about that while the influence of heat difference is greater in low latitudes that of difference of centrifugal force is more powerful in high latitudes. If then the earth were a uniform solid spheroid, there would be a belt of low pressure round the equator and two areas of low pressure at the poles with high-pressure belts between. In the colder regions, however, the air over the open sea is as a rule warmer as well as moister than that over ice or land masses. Tracts of open sea in high latitudes are therefore characterised by abnormally low pressure. Accordingly we find in the North Atlantic and Pacific two areas of low pressure imposed upon the regular decrease of pressure from the horse latitudes to the North Pole itself. Similarly in the Southern Hemisphere the open circum-antarctic sea gives rise to a circle of abnormally low pressure. Beyond, in the region of Antarctic land and ice, the pressure is probably somewhat higher, representing the normal low pressure of the pole.

There are some minor points on which a word of explanation might have been added for the benefit of English readers. For instance, on page 509 we find the word "billion" used in the popular American sense of a thousand million instead of the square of a million, according to the usage of mathematicians, though, curiously enough, in a quotation from Sir John Herschell, on the very next page, a trillion is employed correctly, without comment, for the cube of a million. On page 613 we are told that the "English" unit of pressure gradient is a hundredth of an inch in seventeen miles, which appears a very unreasonable convention in the absence of the explanation that it is equivalent to one millimetre in a degree.

These however are minor matters. The book as a whole is excellent, and the best testimony to its value is the keen interest it has awakened in every student in whose hands it has been placed.

JOHN W. EVANS.

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